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Acta Pædiatrica **44**: 293—301. July 1955

Aus der Kinderklinik der Palacký-Universität, Olomouc, ČSR
(Vorstand: Doz. Dr. A. MORES)

Schnelle Realimentation bei schwerer Dyspepsie und Toxicose im Säuglingsalter

von M. JADRNÍČEK und A. MORES

Einleitung

Schnelle Realimentation bei Säuglingsdurchfallerkrankungen weicht in ihrem Verfahren von der traditionellen diätetischen Therapie ab. Es ist daher kein Wunder, dass sie mancherorts Meinungsverschiedenheit hervorrief, und dass auch noch heute Einwendungen erhoben werden, allerdings nicht von so grundsätzlicher Art wie früher, als ihr sogar Unkenntnis der elementaren Voraussetzungen bei der Säuglingsernährung zu Lasten gelegt wurde. In den letzten Jahren änderten sich jedoch ziemlich die Behandlungsmöglichkeiten, und damit auch das Heil- und Diätverfahren, so dass die schnelle Realimentation bei Säuglingsdyspepsie, analog wie die Vollkost bei Typhus, keinen „Verstoss" mehr bedeutet; sie bietet im Gegentiel den Vorteil, dass sie das Hungern des kranken Kindes einschränkt und auch seinen Aufenthalt im Krankenhaus abkürzt. Den Beweis hiefür liefern sowohl die experimentellen Forschungsarbeiten als auch die gewonnenen Erfahrungen.

Den Antrieb zur schnellen Realimentation gab PARK; HOLT und CHUNG nahmen den Gedanken von neuem auf. CHUNG führte dann in Zusammenarbeit mit VIŠČOROVÁ in Bratislava die klinischen Vergleiche durch. „Therapeutisches Hungern" der an Dyspepsie erkrankten Säuglinge sahen sie als unnötig an, da dieses eher nach dem Aussehen und der Anzahl der Stühle als nach dem Zustand des erkrankten Kindes beurteilt wird. Diese Arbeiten wurden einerseits einer scharfen Kritik unterzogen (FREUDENBERG, DARROW), doch fanden sie anderseits wieder günstige Aufnahme (O'KEEFE, WARTHEN, MITCHELL und Mitarb.).

Es ist klar ersichtlich, dass eine Nahrung mit vollem Kaloriengehalt besonders bei einem dystrophischen Kind seine Bedeutung hat, weshalb die Kritik des therapeutischen Hungerns als berechtigt angesehen werden muss. In der Alltagspraxis wird, wie in allen Lehrbüchern nachgelesen werden kann, beim Diätheilverfahren bei schweren Dyspepsien und Toxikosen die Übergangskost zwischen dem 5. bis 10. Tag und die Vollkost erst nach 2 bis 3 Wochen erreicht. Die gegenwärtigen Möglichkeiten pa-

renteraler Rehydratation schieben jedoch die Diätbehandlung in den Hintergrund und ermöglichen eine schnelle Realimentation, so dass das Kind nicht mehr, wie es früher der Fall war, der Gefahr des Hungerns ausgesetzt wird. Darin liegt das Wesentliche des ganzen Problems der schnellen Realimentation.

Eigene Versuche

Unsere eigenen Erfahrungen mit der schnellen Realimentation stammen aus der Zeit seit dem Jahre 1949, als wir sie versuchsweise und wie es der Zufall brachte niederlegten; erst seit dem Jahre 1952, als wir unsere Erfahrungen erweiterten, konnte stets schnell realimentiert werden. Im Laufe dieses ganzen ersten Jahres wurden alle schweren Fälle von Dyspepsie und alimentärer Intoxikation, sobald sie in die Klinik eingeliefert wurden, wechselweise schnell und langsam realimentiert, um Vergleichsmaterial zu gewinnen; im nachfolgenden Jahr 1953 gingen wir bei allen schweren Durchfallerkrankungen nur noch schnell vor. Bei allen Patienten wurde die bakteriologische Untersuchung des Stuhles und des Halsausstriches ohne spezifischen Infektionsbefund durchgeführt; allen wurden Antibiotica, möglichst der bakteriologischen Empfindlichkeit entsprechend, gereicht.

In den Jahren 1952–1953 wurden im ganzen 171 Säuglinge mit schweren Durchfallerkrankungen behandelt (Tabelle 1). Darunter waren 144 schwere Dyspepsien und 27 Intoxikationen. Von diesen wurden 120 schnell und 51 langsam realimentiert. Es starben 6 Säuglinge, 3 bei langsamer und 3 bei schneller Realimentation, aber nur bei einem Säugling war die akute Durchfallerkrankung die wirkliche Todesursache. Die Patienten wurden in zwei Gruppen eingeteilt: in die erste Gruppe reihten wir die nicht rückfälligen Kranken ein, um das Ergebnis der schnellen Realimentation im Vergleich zur langsamen Realimentation beurteilen zu können; in die zweite Gruppe die rückfälligen Kranken, um festzustellen, ob die schnelle Realimentation auf das Entstehen des Rückfalles von Einfluss ist.

Ohne Rückfall verlief die Durchfallerkrankung bei 130 Säuglingen. Davon wurden 98 schnell und 32 langsam realimentiert. Die parenterale Rehydratation erforderte bei beiden Untergruppen 1 bis 2 Tage und sie verlängerte sich nur in einzelnen Fällen, wegen Erbrechens oder Verweigerung der Nahrungsaufnahme, auf 3 bis 4 Tage.

Bei der *schnellen Realimentation* verfuhren wir wie folgt: nach gründlicher Rehydratation erfolgte das Realimentieren der Kinder im Alter über 3 Monate direkt mit $^2/_3$ „Sunar“ (Trockenmilch) oder $^2/_3$–$^1/_1$ „Relakton“ (saure Trockenmilch), im Alter unter 3 Monaten oder bei Atrophikern mit $^1/_1$ „Lakton“ (Trockenbuttermilch).

und soweit es sich um Brustkinder handelte, wurden sie gleich regelmässig gestillt. Die Nahrungsmenge wurde niemals begrenzt und richtete sich ausschliesslich nach dem Appetit des Kindes. Diese volle Diätkost, wie wir sie nannten, bekamen fast $^3/_4$ der Kinder gleich nach vorgenommener Rehydratation, manchmal sogar bereits am zweiten Tage; wenn aber Appetitlosigkeit bzw. Speien andauerte, wurde dem Kind am nächsten Tag noch Tee oder Karottensuppe, am besten mit Sol. Darrow gereicht und die Realimentation demzufolge um diese Zeitspanne verschoben. Eine solche eintägige Verzögerung war bei $^1/_4$ der Kinder erforderlich, 2 Tage wurden nur in Einzelfällen benötigt (2 Kinder). So erhielten alle schnell realimentierten Kinder gleich am ersten Tag der Realimentation volle Diätkost und durch ihre weitere schnelle Aufreicherung die dem Alter entsprechende Vollkost durchschnittlich am 5. Tag der Realimentation. Für manche Kinder bedeutete die volle Diätkost bereits die ihrem Alter entsprechende Ernährung.

Die *langsam realimentierten* Kinder erhielten nach parenteraler Rehydratation und zum grössten Teil nach einer eintägigen Tee- oder Karottensuppe-Pause am ersten Tag auf $^1/_3$ verdünnte Milchnahrung, die in den folgenden Tagen fortlaufend um je ein Drittel aufgereichert wurde. Diese Kinder erhielten, im Gegensatz zu den schnell realimentierten Säuglingen, die volle Diätkost um 4 Tage später, durchschnittlich am fünften Tag, und volle ihrem Alter entsprechende Kost um 6 Tage später, durchschnittlich am elften Tag der Realimentation.

Bei beiden Realimentationsverfahren musste in den ersten Tagen nach der Rehydratation bei den meisten Kindern wegen noch vorhandener Unlust zum Trinken eine positive Wasserbilanz durch *Ergänzungsinfusionen* aufrechterhalten werden.

Als Beispiel der schnellen Realimentation führen wir 2 Säuglinge an.

1. Alimentäre Intoxikation bei einem einmonatigen, künstlich ernährten, ausgetragenen Säugling (Abb. 1). Die Erkrankung dauerte 1 Tag, das Kind hatte ungefähr 15 wässerige Stühle und erbrach nach jedem Essen, auch nach Tee; es verlor 500 g. Bei der Einlieferung wog es 2900 g (weniger als sein Geburtsgewicht), es war stark dehydriert, hatte erhöhte Temperatur und sein Atmen war vertieft. Nach eintägiger Rehydratation wurde es trotz des noch wässerigen grünen Stuhls sofort mit vollem „Lakton" realimentiert. Es trank gut, so dass es keine ergänzenden Infusionen benötigte. Der Stuhl war am 4. Tag geregelt und das Kind wurde nach 9 Tagen mit einer Gewichtszunahme von 650 g entlassen.

2. Das zweite Kind war ein sieben Monate alter Säugling, ebenfalls mit Zeichen schwerster Intoxikation (Abb. 2). Nach zweitägiger Rehydratation konnte der toxische Zustand als geregelt angesehen werden und am 3. Tag wurde es gleich mit $^2/_3$ Trockenmilch realimentiert; dabei waren noch zwei Tage lang Ergänzungsinfusionen erforderlich. Der Stuhl regelte sich am 4. Tag. Das Kind wurde nach 12 Tagen mit einer Gewichtszunahme von 800 g entlassen.

Wenn wir den *Verlauf* der Durchfallerkrankungen *bei schneller Realimentation mit dem Fortschreiten beim langsamen Realimentationsverfahren vergleichen*, so ist zu ersehen, dass die Gewichtszunahme und die Gewichtskurve beider Gruppen nahezu gleich waren; doch bei schneller Realimentation gelangte man um 4 Tage früher zur Besserung der Stühle und zur Rückkehr der Trinklust. Diese Vorgänge regelten sich bei beiden Realimentationsverfahren parallel mit dem Fieberanfall, d. h. mit der Unter-

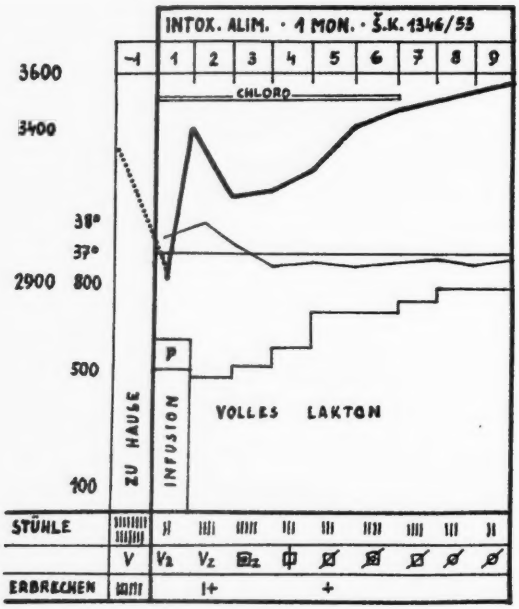

Fig. 1.

drückung der Infektion. Die schnelle Realimentation wies auch durchschnittlich eine um 8 Tage verkürzte Behandlungsdauer auf.

Es kann mit Sicherheit gesagt werden, dass die schnelle Realimentation sowohl in Fällen von Toxikose als bei schwerer Dyspepsie gut vertragen wurde; allerdings ist der Erfolg eng mit einer vollkommenen Rehydratation und mit der Unterdrückung der Infektion verbunden. Wenn diese beiden Grundbedingungen ausser acht gelassen werden, kann bei schneller Realimentation leicht einem Misserfolg begegnet werden, ebenso wie sich anderseits bei konsequenter Durchführung derselben keine Schwierigkeiten ergeben, wenn *gleich nach der Rehydratation* die dem Alter des Kindes entsprechende *volle Säuglingsnahrung* gereicht wird. Dieses Verfahren belegen wir mit folgendem Beispiel (Abb. 3):

Ein fünfeinhalb Monate alter Säugling mit Dyspepsia gravis mit wässerigem Stuhl. Dehydratation und Gewichtsverlust von etwa 500 g wurde innerhalb von 30 Stunden rehydriert. Obwohl es noch dünnflüssigen Stuhl hatte, jedoch nicht erbrach, wurde sofort mit der vollen Säuglingskost mit „Relakton", welche noch 2 Tage lang mit Tropfeninfusionen ergänzt wurde, begonnen. Die Gewichtskurve begann nach einem kleinen Postrehydratationsabsinken anzusteigen.

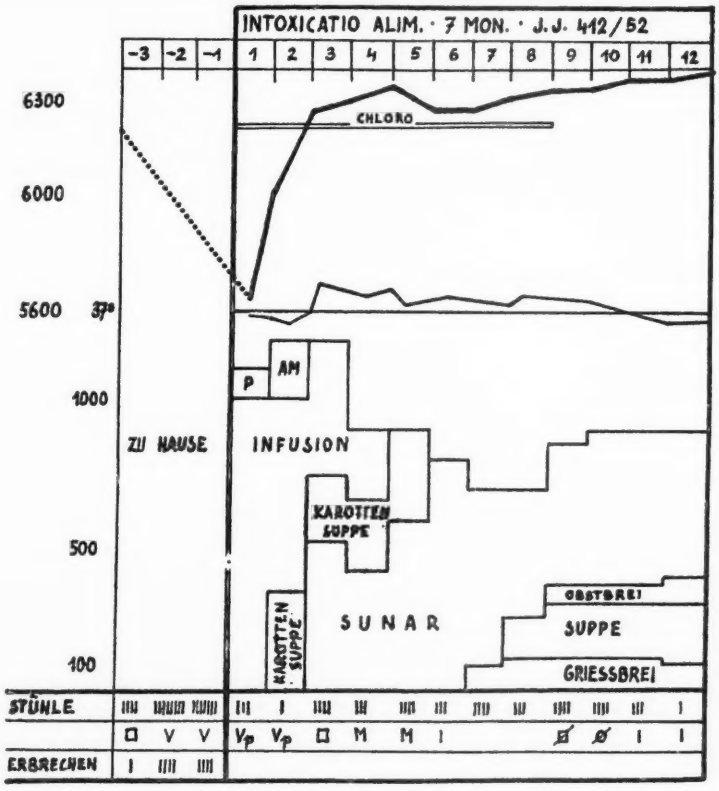

Fig. 2.

Um die Wirkung einer schnellen Realimentation bewerten zu können, ist auch die Beurteilung der Häufigkeit der *Rückfälle* notwendig (Tab. 1). Bei allen *51 langsam realimentierten* schweren Durchfallerkrankungen kam es bei 19, d. h. bei 37 % zu Rückfällen. Der Rückfall trat am 4. bis 10. Tag ein. Obwohl nur $^1/_3$ Relapszustände mit Komplikationen verbunden waren, konnte fast bei allen ein Andauern der Temperatur bis zum Rückfall beobachtet werden, bei mehr als der Hälfte war das Aussehen der Stühle fortdauernd hässlich, die Hälfte der Kinder hörte nicht auf zu erbrechen. So wurde bei der Mehrheit der Fälle der Rückfall nicht durch eine neue Infektion hervorgerufen, sondern durch die ursprüngliche nicht unterdrückte Infektion. Von *120 schnell realimentierten* Säuglingen hatten 22 einen Rückfall, d. h. 18 %, am 4. bis 18. Tag der Erkrankung. Die Hälfte dieser Fälle wies einen Verlauf mit Komplikationen auf. Auch da

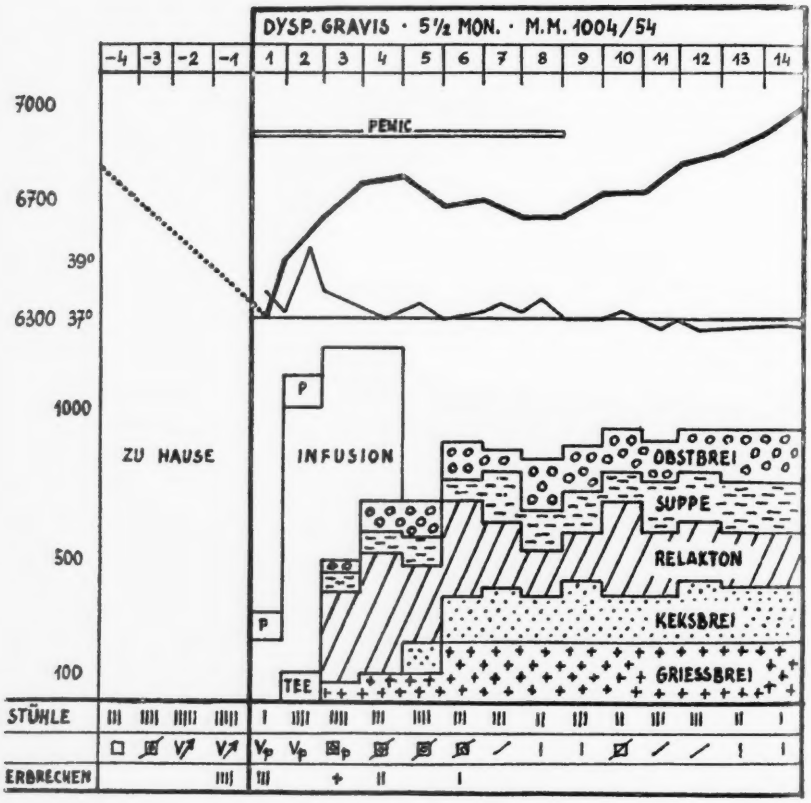

Fig. 3.

hatten 14 Kinder bis zum Rückfall noch keinen gebesserten Stuhl, die erhöhte Temperatur hielt bei 11 von ihnen an. Die Ursache muss daher gleichfalls im Fortschreiten der ursprünglichen Infektion gesehen werden. Die Realimentation im Rückfall wurde „der Sicherheit wegen" bei 8 Kindern langsam vorgenommen (das war noch im ersten Versuchsjahr), trotzdem kam es bei zwei Säglingen zu einem neuem Rückfall. Die übrigen 14 Kinder wurden zum zweitenmal schnell und mit Erfolg realimentiert. Bei schnell realimentierten Fällen ergaben sich vielleicht weniger Rückfälle deswegen, weil die Infektion zufälligerweise rascher überwunden wurde, denn dort, wo dies nicht gelang, traten ebenfalls Rückfälle in Erscheinung. Die Häufigkeit der Relapse hing weder vom Gewicht des Kindes noch von seinem Ernährungszustand ab; ebenso war es gleichgültig, ob da

TABELLE 1.

Übersichtliche Einteilung der bei schwerem Durchfall schnell und langsam realimentierten Säuglinge.

1952–1953		Insgesamt	Ohne Rückfälle		Mit Rückfällen		Gestorben
				davon mit Komplik.		davon mit Komplik.	
Langsame Realimentation	Dysp. gravis	38	23	12	15	6	2
	Toxikose	13	9	2	4	1	1
		51	32	14 / 44 %	19 / 37 %	7 / 37 %	3 / 5.9 %
Schnelle Realimentation	Dysp. gravis	106	87	20	19	10	—
	Toxikose	14	11	3	3	1	3
		120	98	23 / 24 %	22 / 18 %	11 / 50 %	3 / 2.5 %
Insgesamt	Dysp. gravis	144	110	32	34	16	2
	Toxikose	27	20	5	7	2	4
		171	130	37 / 28 %	41 / 24 %	18 / 44 %	6 / 3.5 %

Kind langsam oder schnell realimentiert wurde. Aber es ist klar ersichtlich, dass sie von der Art und Intensität der ursprünglichen, weiter andauernden, noch nicht überwundenen Infektion abhing.

Schlussätze

Unsere Beobachtungen lassen daher eindeutig ersehen, dass die schnelle Realimentation dem Genesungsvorgang der Durchfallerkrankung auch in den schwersten Fällen auf keinen Fall schädlich ist, und dass ihre wesentlich günstigeren Resultate ihr den Vorrang vor der langsamen Realimentation geben, oder streng genommen ihr wenigstens gleichen. Die Besserung des Durchfallzustandes sowie des Gesamtzustandes und die Behandlungsdauer, wenn wir bei der Beurteilung äusserst nüchtern und kritisch vorgehen, stehen mindestens auf gleicher Stufe mit den Ergebnissen der langsamen Realimentation; in Wirklichkeit waren sie jedoch besser. Dabei liegt der Vorteil der schnellen Realimentation darin, dass das Kind keinem unnützen Hungern und keiner Dystrophie, besonders bei andauernder Essunlust, ausgesetzt wird, da ihm früher und mehr Nahrungsstoffe zugeführt werden. Dieser Vorzug fällt besonders bei dystrophischen oder sogar atrophischen Kindern ins Gewicht. Der Erfolg schneller Realimentation ist jedoch unerlässlich an folgende Bedingungen gebunden:

1. Es ist unbedingt notwendig, dass das Kind vorerst vollkommen rehydriert und detoxiziert wird, und

2. dass bei der Realimentation, solange die Essunlust andauert, die Notwendigkeit der Erhaltung einer positiven Wasserbilanz durch Verabreichen

kleiner Infusionen auch auf die Dauer mehrerer Tage nicht ausser acht gelassen wird, sobald der Zustand des Kindes es erfordert.

Dann erweist sich das als gut möglich, was vor der Ära der Antibiotica und der parenteralen Rehydratation und Ernährung unmöglich war und was Freudenberg als „das Maximum des ernährungstherapeutischen Radikalismus" und „ernährungstherapeutischen Nihilismus" nannte.

Zusammenfassung

Schnelle Realimentation wurde 2 Jahre lang bei 120 Säuglingen mit alimentären Intoxikationen und schweren Dyspepsien vorgenommen. Unmittelbar nach der Rehydratation erhielten Kinder im Alter unter 3 Monaten und Atrophiker $^1/_1$ trockene Buttermilch oder Allaitement mixte, Kinder über 3 Monaten $^2/_3$ Trockenvollmilch oder saure Trockenvollmilch, event. ältere Kinder gleich eine volle Säuglingskost. Regelung der Stühle sowie Trinklust wurden früher erzielt und die Behandlungszeit war kürzer als bei der langsam realimentierten Vergleichsgruppe, bei gleicher durchschnittlicher Gewichtszunahme. Schnelle Realimentation ergab keine grössere Anzahl Rückfälle. Soweit sie sich einstellten, muss als ihre Ursache die noch nicht überwundene ursprüngliche Infektion, keinesfalls aber die Art der Realimentation angesehen werden. Der Erfolg der schnellen Realimentation ist aufs engste verknüpft mit einer vollkommenen Rehydratation, Detoxikation und mit dem Erhalten einer positiven Wasserbilanz durch Verabreichen kleiner Infusionen, soweit die Essunlust andauert. Die Resultate beweisen, dass eine schnelle Realimentation dem Genesungsvorgang der Durchfallerkrankung keinen Schaden zufügt. Die günstigeren Ergebnisse geben ihr den Vorrang vor der langsamen Realimentation. Ihr vorteil liegt darin, dass besonders bei andauernder Appetitlosigkeit das Kind keinem überflüssigen Hungern und keiner Dystrophisierung ausgesetzt wird.

Rapid Realimentation in Infants suffering from Severe Diarrhea and Toxicosis.

Study on 120 infants. Immediately after rehydration, infants below 3 months of age received evaporated buttermilk or mixed feeding; infants over 3 months of age, evaporated fullmilk or dried acid whole milk. The stools were more rapidly normalized, the anorexia improved and the period of treatment shorter than in a control group given gradual realimentation. There were no harmful effects from the rapid alimentation.

Réalimentation précoce chez des enfants souffrants de diarrhés graves et de toxicoses.

120 enfants ont été examinés. Immédiatement après la hydratation, les enfants âgés de moins de 3 mois ont reçu du babeurre évaporé ou allaitement mixte. Les enfants ayant plus de 3 mois ont reçu du lait évaporé ou du lait acid. Les selles étaient normalisées, l'appétit amélioré plus rapidement et la période de traitement était plus courte que dans le groupe de contrôle recevant réalimentation graduelle. Il n'y a eu aucun accident causé par l'alimentation rapide.

Realimentación rápida después de diarreas severas y toxicosis.

Se estudiaron 120 miños. Inmediatamente a la hidratación, los menores de tres años recibieron babeurre evaporado, los mayores de esa edad, leche completa o leche acidificada evaporada. Las deposiciones se normalizaron, la anorexia cedió mas rápidamente y el período de tratamiento fué mas corto que en el grupo control, al cual se realimentó gradualmente. No hubo accidentes imputables a la realimentación rápida.

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Kinderklinik der
Palacký-Universität
Olomouc, ČSR

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From the Pediatric Clinic (Head: Professor A. WALLGREN) and the Children's Surgical Department (Head: Docent T. EHRENPREIS), Karolinska Sjukhuset, Stockholm

Follow-up Investigation of Children with Ulcerative Colitis

With Special Reference to Indications for Surgical Therapy

by R. LAGERCRANTZ

In recent years ulcerative colitis has become more common in Swedish children. Because of its chronicity and high incidence of recurrence the disease constitutes a current problem (WALLGREN). It was therefore considered warranted to re-examine a series of patients with ulcerative colitis reported by the writer in 1949, with the object of assessing the effect of therapy, particularly antimicrobial drugs. The frequent success of modern single-stage colectomy and ileostomy (BROOKE, PERMAN, STRÖMBÄCK) motivates discussion of the indications for such surgery.

Materials and Methods

The greater part of the clinical material consisted of the 134 children described by the writer in 1949.[1] Concerning the accepted diagnostic criteria and the composition of the original series the reader is referred to that study. To these cases have been added 16 children hospitalized later at the Pediatric Clinic of Karolinska Sjukhuset and followed up for at least three years after the onset of ulcerative colitis. All 16 presented the typical picture of sanguino-purulent diarrhoea for long periods, loss of weight and, as a rule, anaemia. Table 1 shows the most important data from these cases. Fig. 1 shows the ages of all the children at the onset of their disease.

According to the classification employed by HAWKINS, RICE-OXLEY & TRUELOVE, IHRE, etc. the children could be grouped as indicated below (only those observed for more than two years are included):

Group	Course of disease	No. of patients and % of total
1.	Acute fulminating: a single attack going on to death in less than 1 year	2 (1.5 %)
2.	Chronic intermittent: more than one attack, with at least several weeks' complete remission between attacks	108 (78.8 %)[2]
3.	Chronic continuous: continuous symptoms for more than one year	17 (12.4 %)
4.	Single attack: followed by complete remission	10 (7.3 %)
		Total 137

[1] Five cases from the 1949 series have been excluded from this study. Four of them (Cases 38, 46, 54 and 57 in the original report) failed on renewed examination to comply accurately with the diagnostic criteria. In the fifth (Case 77) the diagnosis was later altered to hepatic and splenic disease, probably primary, with portal stasis. The intestinal symptoms disappeared after splenectomy and vascular anastomosis.

[2] The classification of some patients is doubtful, as they often appeared to conceal symptoms. Some of the patients in group 2 probably were not completely free from symptoms between attacks of the disease, but the intensity of their symptoms varied greatly.

TABLE 1

Major data in 16 fresh cases of ulcerative colitis treated at Karolinska Sjukhuset 1950–1954.

	No. of patients
Age at onset:	
3–7 years	6
8–15 „	10
Proctoscopy:	
Pathologic findings	16
Roentgenographic examination:	
Probably normal	1
Pathological changes in part of colon	4
„ „ „ entire „	11
„ „ „ „ „ and lower part of ileum	2
Haemoglobin, minimum reading:	
< 11 g %	16
< 8 g %	9
Severity of disease:	
(See LAGERCRANTZ)	
I (Mild)	1
II (Moderate)	9
III (Severe)	6
Period of observation:	
> 3 years	16
> 5 „	3

The patients or their nearest relatives were given a questionnaire. This was completed in all but 17 cases. These 17 have been included in the study for as long as they could be followed up. In the fatal cases the hospital records, including any autopsy notes, were reviewed.

Results

As usual, the commonest manifestations of ulcerative colitis in these children were diarrhoea, fatigue and loss of weight. Anaemia was present in most of the serious cases. Haematologic studies were carried out in some children (BARR, DELAVA & ZETTERSTRÖM).

As a rule, the course of the disease was markedly remittent or intermittent. It was frequently surprising that patients with appreciable symptoms were able to work and lead a relatively normal life.

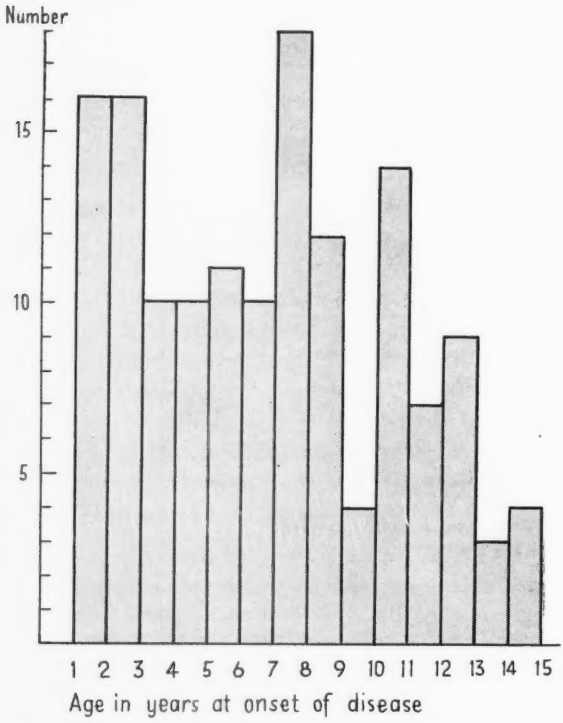

Fig. 1. Ages at onset of disease for all children followed up for more than two years.

In replying to the questionnaire most of the patients stressed the importance of psychogenic factors. These and infections of the upper respiratory tract were stated to be the commonest causes of recurrence. The majority of the children with ulcerative colitis admitted to the Pediatric Clinic in recent years were examined by a children's psychiatrist (Dr. E. B. Nordlund). Many of them were thereby found to be maladjusted; some came from unsuitable environments and a few showed psychogenic manifestations (probably) of a more constitutional type. In some cases the contact with the psychiatrist and relatively simple measures were sufficient to improve the child's adjustment. In a few severe cases (e.g., the colectomized child described later in this paper), more intensive therapy effected considerable improvement in the mental condition and acceptance of the disease with later ileostomy.

In their written replies most of the patients also maintained that they felt better on ordinary diet than on a strict regimen. It is notable that many

reported beneficial results from an uncooked vegetarian diet. Some patients ascribed to such a diet the greatest importance for improvement in their condition. A fairly large number of patients stated that they took small doses of sulphonamides regularly or during periods of diarrhoea (as a rule salicylazosulphapyridine–salazopyrine; azulfidine[R] 1–0.5 g 1–3 times daily), and considered such medication indispensable.

Involvement of the entire colon and the terminal portion of the ileum together with a progressive anaemia generally indicate an unfavourable prognosis (LAGERCRANTZ). That such patients may nevertheless become asymptomatic is illustrated by the following case history: A six year-old boy developed severe ulcerative colitis which recurred repeatedly for 18 years. From time to time the patient had severe anaemia (minimum haemoglobin reading 35 per cent). Roentgenographic studies showed ulceration of the entire colon and the lower ileum. This patient has now been asymptomatic for six years. In several similar cases (Nos. 33, 41, 69, 80 and 102 in the 1949 series) surprising improvement or apparent recovery was recorded.

On the other hand, patients who have been asymptomatic for many years may die of carcinoma of the colon at an early age. (A 22-year-old man died of metastizing carcinoma of the colon after having been free from intestinal symptoms for nine years.)

It is difficult to determine when the disease has definitely healed. In some of the patients who wrote that they had been asymptomatic, closer questioning elicited a description of symptoms. In some cases, too, thorough clinical examination (including proctoscopy and roentgenographic studies) gave positive findings in the absence of subjective discomfort.

Serious recurrence, however, is relatively rare after two years without symptoms. This was demonstrated in the 1949 investigation. Of the patients who at that time had been asymptomatic for at least two years only four developed pronounced symptoms later on. For this reason all the patients observed for two years or more have been grouped according to their condition at the time of follow-up (Table 2). It is seen that 44 (32.2 per cent) had been asymptomatic for at least two years. Sixty-two (45.2 per cent) had been free from symptoms for a shorter time or had mild or moderate (as a rule intermittent) discomfort, but were able to live fairly normally and work or attend school. Twelve patients (8.8 per cent) were disabled by the disease. Some of these were in hospital at the time of follow-up. Several had carried on working to an extent surprising in view of their fatigue and diarrhoea. Nineteen patients (13.8 per cent) had died of ulcerative colitis or other diseases.

The causes of death in the ten fatal cases prior to 1949 have been reported

TABLE 2

Duration of ulcerative colitis in relation to condition at follow-up.
(All patients observed for at least two years.)

Duration of disease (years)	A Asymptomatic for 2 years or more	B Symptoms during last 2 years (not bedridden)	C Severe symptoms	D Dead	Total
½– 1	14	—	—	2	16
> 1– 3	8	6	—	1	15
> 3– 6	7	13	3	6	29
> 6– 9	8	7	2	1	18
> 9–14	5	24	2	4 (2)	35
>14–26	2	12	5	5 (3)	24
Total	44	62	12	19 (5)	137
%	32.2	45.2	8.8	13.8	

The figures in parentheses denote the number of deaths from carcinoma of the colon. A further patient with colonic neoplasm is still alive after colectomy.

in the earlier study. Four of the nine later deaths were due to carcinoma of the colon, three to progressive ulcerative colitis, one to operation for renal calculi and one to leukaemia. In two of the patients with progressive colitis ileostomy had been performed. In the two patients whose major pathology was nonintestinal the colonic lesions had not healed. A survey of all the fatal cases is given in Table 3.

The patients who died of ulcerative colitis had been ill for varying periods (Table 2). Twelve died within ten years of the onset of the disease. All of the six patients who developed carcinoma of the colon had had symptoms of ulcerative colitis for more than ten years.

Eleven patients underwent surgical procedures (Table 4). In three of the patients with carcinoma of the colon laparotomy showed the growth to be nonresectable. One patient is alive six years after colectomy for cancer. The two above-mentioned deaths from progressive colitis after ileostomy occurred within a year of operation. In the last two years five patients have undergone single-stage ileostomy and subtotal colectomy. The results are encouraging. The following patient has been observed for 18 months after operation and the others for shorter periods.

A nine-year-old girl (Case 133 in the 1949 series) became acutely ill with high fever and diarrhoea. For long periods she was bedridden and had severe weight loss and moderate anaemia. The ulcerative process extended over the entire colon and the terminal ileum. There was a distinct psycho-

TABLE 3

Causes of death among 137 patients with ulcerative colitis followed up for at least two years.

	No. of deaths	
Ulcerative colitis or its complications .	14	
[Carcinoma of the colon, 6 cases—4.4 %	5]	12.4 %
(One patient alive after colectomy) .		
[Cirrhosis of the liver	2]	
Ulcerative colitis + other disease	3	
Other disease	2	
Total	19 (13.8 %)	

TABLE 4

Surgical procedures in ulcerative colitis.

Operation	No. of patients	Deaths
Laparatomy (inoperable carcinoma of the colon)	3	3
Ileostomy	2	2
Ileostomy + colectomy	6	0
Total	11	5

genic component which necessitated psychotherapy for several years. This resulted in reduced tension and improved adjustment. The intestinal symptoms, however, recurred at intervals with increasing severity. In the spring of 1953, when the patient was 15 years old, she was very ill and emaciated. Puberty had not commenced. The roentgenograms showed scar contraction of part of the colon. In June of the same year subtotal colectomy with ileostomy was performed. The postoperative course was uneventful. In six months her weight increased by more than seven kilograms, secondary sex characteristics developed, menstruation commenced and her mental state was satisfactory. Three months later she began a professional training course. At follow-up examination, one and a half years after operation, her general condition was excellent. She weighed 18 kg more than prior to operation. Her ileac stoma functions well on a normal diet (the faeces are semisolid). The blood values are normal. At times there is insignificant anal secretion of mucus.

Neither psychiatric nor surgical therapy was extensively employed in this series. Many of the patients, however, were given intensive therapy

with antibiotic and chemotherapeutic drugs (LAGERCRANTZ). As general measures were always employed concurrently and placebo controls were lacking, an exact evaluation of the effect of medication is not possible. It seemed, nevertheless, that antimicrobial drugs (sulfa compounds, chloramphenicol, terramycin) frequently gave relief in acute exacerbations and in relapse of the disease. The most effective drug appeared to be salazopyrine (azulfidine^{R}), which was also the preparation most frequently employed. On the other hand, progression could occur despite such medication. In order to obtain figures reflecting the significance of antimicrobial drugs for the long-term prognosis of ulcerative colitis, comparison was made of cases with and without such therapy (Table 5). Group B in this table comprises patients given adequate dosage of salazopyrine for at least one month during the first year of illness (about 0.5 g six times daily for older children and about half this dosage for younger children). In some cases medication was stopped when the child's condition improved after a few weeks or, more commonly, was given in reduced dosage. Recurrence of the disease in these children was as a rule also treated with salazopyrine. Group A consists of patients who received no antimicrobial drugs. The comparison of these two groups at follow-up examination is discussed below. In the smaller number of patients treated early in the disease with other antimicrobial drugs than salazopyrine (other sulfa compounds, chloramphenicol, etc.) the long-term prognosis was not more favourable.

Discussion

The chronic and relapsing character of ulcerative colitis is illustrated by this follow-up investigation. The appropriateness of classifying the patients into those asymptomatic for at least two years (Group A in Tables 2 and 5) and those who had symptoms but were not bedridden is open to question. Thorough examination of the former group would probably have revealed lesions in some cases. Although the likelihood of manifest symptoms is less in group A than in the other patients, it is not eliminated. The risk of developing carcinoma of the colon at an early age is present in both groups.

The figures in Tables 2 and 3 do not give a complete picture of the personal and social significance of ulcerative colitis. Many of the patients in group A had been severely ill for long periods and many in group B, while not considering themselves disabled, were greatly inconvenienced by their disease. That they were able to work was in some cases a reflection of great willpower.

The commonest causes of relapse in this, as in other series, were infections of the upper respiratory tract and psychogenic disturbances (LAGERCRANTZ).

TABLE 5

Role of chemotherapy for long-term prognosis.

	No.	Period of observation (years)				Haemoglobin min. value			Degree of severity (see LAGERCRANTZ)			Condition at follow-up (see Table 2)			
		2–6	7–11	12–16	17–29	< 50 %	50–70 %	> 70 %	Slight 1	Moderate 2	Severe 3	A	B	C	D
A. No chemotherapy	21	4[1]	1	8	8	7	3	11	7	9	5	15	2	—	4
B. Early chemotherapy	34	12	18	4	—	8	17	9	3	22	9	8	20	3[2]	3[3]

[1] 2 patients died during the first year of disease.

[2] 1 patient operated on recently with colectomy and ileostomy.

[3] 1 patient died of other disease while still showing symptoms of ulcerative colitis.

It was also shown that strict dieting and long periods of bedrest were unsuitable. The classification of the series according to the length of the observation period (Table 2) shows that in some cases there was a tendency to improvement after many years, even if the change frequently consisted of better psychosomatic adjustment rather than actual healing. Patients who had had ulcerative colitis for more than nine years, however, seldom became asymptomatic.

The classification of ulcerative colitis accepted by many workers and also employed in this study (p. 302) is partly based on prognostic considerations. The patients with a single attack followed by complete freedom from symptoms (Group 4) naturally had the most favourable prognosis. In all such cases in this study the observation period exceeded 5 years and in many cases 10 years. The late results were somewhat poorer in the group with chronic continuous symptoms (Group 3) than in cases with chronic intermittent symptoms (Group 2), but the difference was not significant with regard to mortality or degree of symptoms at follow-up.

In comparing the present series with those of other writers, e.g., the adult patients of RICE-OXLEY & TRUELOVE, SLOAN, BARGEN & GAGE, and IHRE, or the child patients of JACKMAN, BARGEN & HELMHOLZ, it is important to consider this classification of the disease. Most of the British and American studies, particularly those including children, contain a much larger proportion of acute, fulminating cases (about 20 per cent) than in the series here reported (1.5 per cent). This is the most likely explanation of the better results in these patients, despite the long period of observation, than in the majority of studies on children.

The most common cause of death in the first ten years after the onset of ulcerative colitis was progression of the disease (nine cases). Hepatic cirrhosis accounted for two cases and one patient died of unrelated disease. Of the seven patients who died more than ten years after the commencement of colitis, five had carcinoma of the colon. One died of progressive colitis and one of unrelated disease.

The frequency of carcinoma of the colon in this study (4.4 per cent) tallies well with the figures from other large series. SVARTZ (1951) reported that of 115 patients in whom ulcerative colitis appeared before the age of twenty, 4.3 per cent developed carcinoma of the colon. CALLAGHAN reviewed 6,890 colitis patients of all ages in the literature and found that this malignancy occurred in 3 per cent. Thus the frequency of colonic cancer in persons with ulcerative colitis is many times that in a cross section of the population of corresponding age. In this, as in previous reports, the risk increased with the duration of the colitis.

The two deaths from progressive ulcerative colitis after ileostomy suppo

the modern opinion that ileostomy alone is inadequate. It should be combined with colonic excision, preferably in a single stage operation (BROOKE, STRÖMBÄCK, PERMAN, and others). The technique of operation and of care of the stoma have substantially improved. Writers such as BROOKE, STRÖMBÄCK, PERMAN, FERGUSON and FIERST have described good results with primary mortality ranging from one to six per cent.[1] Most of the patients in these writers' series improved rapidly after operation, gained much weight and soon became fit for work. Some married and several gave birth to children. The mental improvement frequently was so great that it was advanced as an argument against psychogenic factors being the primary cause of ulcerative colitis.

The favourable results of single-stage colectomy with ileostomy are illustrated by the five cases in the present study. In all of them operation was undertaken to relieve severe, progressive ulcerative colitis. In two cases there was a clear tendency to colonic constriction. Despite the fact that the operation entails a permanent ileac stoma it is felt that the beneficial effects warrant extension of the indications for such treatment. In most cases the ideal closure of the stoma and sigmoidal or rectal anastomosis of the ileum is unattainable. Some surgeons consider that in many cases extirpation of the rectum is also advisable (BROOKE).[2]

When assessing the disadvantages of ileostomy in growing children, not the least in girls (four of the five patients in the present investigation were girls), one must take into account the poor preoperative condition with delayed sexual development. Ileostomy is well accepted by patients who have been severely ill.

As patients who have had manifest symptoms of ulcerative colitis for more than nine years seldom become asymptomatic (Table 2) and, further, run an appreciable risk of early death from carcinoma of the colon (Tables 2 and 3), they should receive consideration for surgery. When the colitis is of shorter duration operative intervention may be contemplated in the presence of uncontrollable symptoms and long periods of invalidity. A pronounced tendency to anaemia and the occurrence of hepatic complications indicate a poor prognosis (LAGERCRANTZ), and should be taken into consideration when deciding for or against surgery. If there is constriction of the bowel or pseudopolyposis, colectomy should be undertaken with the least possible

[1] ROGERS, BARGEN & BLACK reported the early and late results in 124 patients with ileostomy. The results were poor and BARGEN, in an editorial in the same issue of *Gastroenterology*, recommended restricted indications for the surgical treatment of ulcerative colitis. Since most of the patients had been treated with ileostomy alone, however, the results cannot be said to contraindicate the modern method of ileostomy *plus* colectomy.

[2] In one of the four patients in this study the rectum was later excised because of persistent bleeding.

delay. Other surgical indications discussed in the literature, such as local complications, severe septic states with or without arthritis or pyoderma, and profuse haemorrhage were not seen in the present series.

With regard to the risk of carcinoma of the colon, the advisability may be discussed of regular roentgenographic examination of patients who have had ulcerative colitis for about eight years or more and have not undergone colectomy. In many such patients, however, the detection of an operable neoplasm may be difficult because of the extensively diseased colon.

As earlier stated, some of the children were examined by a psychiatrist and a number received psychotherapy. This was of great value for the patients' acceptance of and adjustment to their disease. The difficulty of influencing the bowel lesions, as such, by psychotherapy was demonstrated by some of the cases in this study. Most psychiatrists who have had experience with ulcerative colitis agree that the psychogenic factors are not easily accessible (for references, see SJÖVALL), As a rule intensive psychotherapy must be continued for years, which may not be without risk and which we were not able to offer the patients here reported. Although there may be reason to react against facile optimism concerning the likelihood of affecting ulcerative colitis by psychotherapy, the mental factors in the disease must not be disregarded. That psychotherapy frequently gives good results for the patients' wellbeing and environmental adjustment has recently been pointed out in Sweden by GUNNARSSON, BASTMAN-HEISKANEN & HARDING, WALLGREN, IHRE, SJÖVALL, and others.

The value of chemotherapeutic and antibiotic agents in ulcerative colitis is difficult to assess. Bedrest and special diet always accompany such treatment and iron therapy, blood transfusion and spasmolytics are also given when indicated. Furthermore, the reports in the literature concern different drugs, and indications, duration of treatment and dosage have varied. Like such writers as IHRE it is the author's impression that antimicrobial therapy often, but not invariably, has a favourable effect on the disease. Salazopyrine would seem to be among the best preparations (e.g. SVARTZ 1954, MORRISON and BARGEN). Many writers are of the opinion that such medication is of minor importance (CALLAGHAN). As controls were not available in the present investigation, scientific evidence of the effect of antimicrobial drugs is lacking.

These drugs have been stated to be less important for the long-term prognosis than for acute exacerbations (COLLINS, RICE-OXLEY & TRUELOVE, LAGERCRANTZ, etc.). It was therefore considered warranted to study their effect on the late results.

In Table 5, comparison is made of patients treated in several hospitals. Although the time of their illness varied, the diagnostic criteria were con-

stant and the general lines of treatment underwent no essential change during the period in question. In the last ten years, however, a fuller diet was given and greater regard was paid to psychological factors. For this reason the children who received no antimicrobial drugs were at some disadvantage. Table 5 shows that the number of severely ill children was greater in the group given such medication early in the disease. This fact operates in favour of the "untreated" group at follow-up. The figures show that even when antimicrobial drugs were given at an early stage, the course of ulcerative colitis frequently was protracted and severe. In each group one patient died of progressive colitis and one of carcinoma of the colon. Two patients in group A died of ulcerative colitis and intercurrent infection. These patients would probably have survived had chemotherapy been available.

That the comparison in Table 5 otherwise favours the patients who did not receive chemotherapy is probably explained by the fact that the illness of these children was on average less severe and of shorter duration than in the treated children. The former group were also observed for longer periods and, as stated in the foregoing, the disease tends to improve after many years.

These findings, therefore, should be assessed with reservations. The table provides an illustration of the condition at follow-up of the children given antimicrobial therapy rather than a comparison with untreated patients. The figures, however, support the general impression at the Pediatric Clinic of this hospital that chemotherapeutics and antibiotics have less influence on the long-term prognosis of ulcerative colitis than on acute exacerbations. We have frequently observed that such therapy does not prevent progression or relapse of the disease. Nor does the literature contain any conclusive proof of a longterm effect of antimicrobial drugs in ulcerative colitis.

Medication with chemoterapeutics should be directed against the intestinal infection. (It is possible that certain preparations such as salazopyrine influence the mode of collagen reaction.) Many writers, e.g. CALLAGHAN, have expressed the opinion that infection by micro-organisms is only a contributory cause of ulcerative colitis. The aetiology of the basic disease is unknown, but research is concentrated on psychogenic factors, on disturbances of the enzymatic system (e.g. STOUGHTON) and anomalies of the ganglion cells (STORSTEEN, KENOHAN & BARGEN) rather than on bacterial causation. In many aspects ulcerative colitis resembles a systemic disease (WARREN & SOMMERS). Many writers have demonstrated similarities to collagenoses in regard to clinical and pathologico-anatomic changes (LEVINE, KARSNER & KLOTZ, SOMMERS, ANDERSON & WARRENS, STREICHER & CATCHPOLE, IHRE and IVEMARK). At this clinic, too, we have seen patients with

verified collagenoses (lupus erythematosus disseminatus or periarteritis nodosa) who also presented the clinical picture of ulcerative colitis (WALLGREN).

The favourable action of ACTH and cortisone described by many writers, such as KIRSNER & PALMER, may also be interpreted as evidence for the view that the disease is a "hypersensitivity reaction". One must keep in mind, however, the antiphlogistic action of these hormones. In the present series ACTH and cortisone were tried only in a few cases. Their chief effects were on the patients' subjective wellbeing. Such therapy may be indicated in certain situations (KIRSNER & PALMER) but should not be regarded as the ultimate answer to the search for effective treatment of ulcerative colitis.

It appears probable that the reason for the relatively unsatisfactory effect of antimicrobial agents on long-term results is that ulcerative colitis is not basically an infectious disease. The conclusion from this study is that the therapeutic possibilities must be improved by intensified research into the aetiology, pathogenesis and treatment of the disease. With the resources now at our disposal ileostomy and colectomy must be advocated for a considerably greater number of cases than hitherto.

Summary

One hundred and thirty-seven patients who fell ill with ulcerative colitis before fifteen years of age have been followed for two to twenty-six years (Tables 2 and 3). Of these 78.8 % had the chronic intermittent type of disease. Nineteen patients died after varying periods (Table 2), seventeen (12.4 %) of ulcerative colitis or its complications. Of those surviving 8.8 % were found to be severely incapacitated on follow-up examinations. Those who had had symptoms for more than nine years seldom recovered (Table 2). Even patients who had been free from symptoms for several years ran the chance of developing cancer of the colon at an early age and in this series the total frequency was 4.4 %.

Operations with modern techniques (combined ileostomy and colectomy) have been performed in five cases with good results (Table 4.) Broader indications for operation seem warranted and surgery is recommended for all severe cases which show incapacitating symptoms for several years without response to medical treatment. Operation should be considered even in moderately severe cases with symptoms for more than eight to nine years, because of the risk of colonic cancer.

There is no proof in this material that early chemo- or antibiotic therapy can influence the long-term prognosis (Table 5). These results correspond with the modern view of the etiology and pathogenesis of the disease. Ulcerative colitis is probably a "hypersensitive reaction" rather than a primary infection.

Psychotherapy is discussed and the conclusion drawn that it is of great importance in the treatment of these patients but that it does not directly influence the pathological process.

The results emphasize the necessity of employing a more active therapy in ulcerative colitis.

L'avenir de 137 enfants atteints de colite ulcéreuse.

Cent trente-sept enfants ayant eu une colite ulcéreuse avant l'âge de quinze ans ont été suivis pendant deux à vingt-six ans. Parmi ceux-ci 78,8 % avaient la forme chronique intermittente de la maladie. Dix-neuf patients sont morts après des périodes variables, dix-sept (12,4 %) de colite ulcéreuse ou de ses complications. En examinant ultérieurement les survivants on trouva que 8,8 % de ceux-ci étaient fortement affaiblis. Ceux qui ont présenté des symptômes pendant plus de neuf ans ont rarement guéri. Même les patients qui ont été exempts de tout symptôme pendant plusieurs années ont couru le risque de développer un cancer du colon à un âge plus rapproché et la fréquence de celui-ci était de 4,4 % dans cette série. Cinque cas ont subi avec succès des opérations suivant des techniques modernes (iléostomie combinée avec une colectomie). Il semble que le traitement opératoire trouve des indications plus larges et celui-ci est conseillé pour tous les cas graves qui, sans répondre à un traitement médical, présentent pendant plusieurs années des symptômes les rendant très faibles. Il faudra penser à l'opération, à cause du danger de cancer du colon, dans les cas moyennement graves présentant des symptômes pendant huit à neuf ans. On n'a pas pu donner la preuve que, dans ce groupe, la chimiothérapie ou un traitement précoce aux antibiotiques, peuvent influencer le pronostic éloigné. Ces résultats correspondent avec les conceptions modernes sur l'étiologie et le pathogénie de la maladie. La colite ulcéreuse est probablement plutót une « réaction d'hypersensibilité » qu'une infection primaire. L'auteur discute de la psychothérapie et conclue qu'elle a une grande importance pour le traitement de ces enfants, mais qu'elle n'exerce pas une influence directe sur le processus pathologique. Les résultats démontrent qu'il est nécessaire d'appliquer un traitement plus actif dans la colite ulcéreuse.

Nachuntersuchung von 137 Kindern mit ulcerativer Colitis.

Einhundertundsiebenunddreissig Patienten, die vor dem Alter von 15 Jahren an ulcerativer Colitis erkrankt waren, wurden während eines Zeitraumes von 2 bis 26 Jahren verfolgt. Von diesen hatten 78,8 % den chronisch intermittierenden Typ der Krankheit. Neunzehn Patienten starben nach verschiedenen Zeiten, siebzehn (12,4 %) an ulcerativer Colitis oder ihren Komplikationen. Von den Überlebenden wurden 8,8 % bei der Nachuntersuchung als schwer beeinträchtigt angesehen. Patienten, die Symptome während mehr als 9 Jahren hatten, heilten selten aus. Auch solche, die während vieler Jahre symptomenfrei waren, liefen das Risiko einer Coloncarcinomentwicklung in frühem Alter, und die totale Frequenz betrug in dieser Serie 4,4 %. Operationen mit moderner Technik (kombinierte Ileostomie und Colektomie) sind in 5 Fällen mit gutem Erfolg ausgeführt worden. Erweiterte Indikationsstellungen zur Operation erscheinen berechtigt und chirurgische Behandlung wird für alle schweren Fälle empfohlen, welche beeinträchtigende Symptome während mehrerer Jahre ohne Ansprechbarkeit für medikamentöse Therapie gezeigt haben. Operation sollte ebenfalls in mässig schweren Fällen mit einer Symptomendauer von mehr als 8 bis 9 Jahren mit Hinblick auf die Gefahr eines Coloncarcinoms erwogen werden. In diesem Material kann kein Einfluss von früher Chemo- oder Antibiotikatherapie auf die Spätprognose bewiesen werden. Diese Resultate stimmen mit der modernen Anschauung betreffend der Ätiologie und Pathogeneses dieser Krankheit überein. Die ulcerative Colitis ist wahrscheinlich mehr eine „Hypersensitivitätsreaktion" als eine primäre Infektion. Psychotherapie wird erwogen und der Schlussatz gezogen, dass sie von

grosser Bedeutung bei der Behandlung dieser Patienten ist, jedoch nicht direkt den pathologischen Prozess beeinflusst. Die Resultate unterstreichen die Notwendigkeit, mehr aktive Therapie bei der ulcerösen Colitis anzuwenden.

Estudio evolutivo de 137 niños enfermos de colitis ulcerosa.

Se estudian 137 pacientes que contrageron colitis ulcerosa antes de los 15 años de edad y que han sido controlados posteriormente en fechas que oscilan entre 2 y 26 años. 78,8 % de ellos presentaron la forma intermitente de esta afección. 19 fallecieron en diferentes períodos, 17 de ellos de colitis ulcerosa o sus complicaciones (12,4 %). Entre los sobrevivientes se encontró, en controles posteriores, que el 8,8 % presentaba severa incapacidad. Aquellos que presentaron sintomatología durante mas de 9 años difícilmente se recuperaron. Aún en pacientes que permanecieron asintomáticos varios años, la posibilidad de contraer cáncer de colon a edad temprana fué en nuestras series de 4,4 %. En 5 casos los resultados operatoris fueron buenos empleando las modernas técnicas quirúrgicas (ileostomía y colectomía combinadas). Se recomienda el generoso empleo de la cirugía en todos los casos graves en que la sintomatología se mantenga varios años sin respuesta al tratamiento médico. Debe pensarse seriamente en el tratamiento quirúrgico en todos los casos que persistan entre 8 y 9 años aunque sean de moderada gravedad ya que en ellos el riesgo de cáncer colónico es serio. En nuestro material no hemos encontrado la prueba que el tratamiento quimioterápico o antibiótico influya sobre el pronóstico alejado. Estos resultados están de acuerdo con las modernas teorías, etiológicas y patogénicas, de esta enfermedad. Probablemente la colitis ulcerosa sea mas una «reaccion de hipersensibilidad» que una infección primaria. Se discute el tratamiento psicoterápico concluyéndose que es de la mayor importancia en estos pacientes aunque no tiene influencia directa sobre el proceso patológico. Los resultados señalan la necesidad de emplear en este mal una terapéutica mas activa.

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Pediatric Clinic
Karolinska Sjukhuset
Stockholm, Sweden

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From the Department of Pediatrics, Kronprinsessan Lovisas Barnsjukhus, the Department of Obstetrics and Gynecology, Karolinska Sjukhuset, and Konung Gustaf V's Forskningsinstitut, Stockholm

Plasma Levels of 17-Hydroxycorticosteroids and Urinary Excretion of 17-Ketosteroids in Normal Children

by C. G. BERGSTRAND and CARL A. GEMZELL

The urinary excretion of 17-ketosteroids in children has been repeatedly investigated during the last fifteen years and the value of such determinations is well established. The estimation of the urinary 17-ketosteroids, however, reflects mainly the androgen production in the adrenals and gives only slight information about the 17-hydroxycorticosteroids produced, and thus no indication of adrenal activity.

The adrenal activity in children may be estimated by the plasma levels of 17-hydroxycorticosteroids. Few investigations concerning the clinical value of this method have been performed in normal children (Ely, Kelley & Raile, Raile, Ely & Kelley and Klein, Papadatos & Fortunato). The purpose of this paper is to present the plasma levels of 17-hydroxycorticosteroids and urinary excretion of 17-ketosteroids in 34 normal children of various age.

Methods and Materials

The determination of the 17-hydroxycorticosteroids in the blood was carried out by the method of Nelson & Samuels. The plasma was separated from the erythrocytes by centrifugation. The magnesiumsilicate-Celite chromatographic column was employed for purification and the micromodification of the colour reaction of Porter and Silber was used for quantitative determination. All the levels of 17-hydroxycorticosteroids are expressed in terms of μg per 100 ml of plasma.

The amount of 17-ketosteroids in the urine was determined by the method of Callow, Callow & Emmens with the modification of Vestergaard. The 17-ketosteroids are expressed in terms of mg per 24 hour sample of urine.

Thirty-four children, 18 girls and 16 boys, 2–15 years of age, were selected at random. All the children had been in the hospital for at least a week and most of them were confined to bed. All children with endocrine disorders were excluded. Most of them were convalescents from tuberculosis or mild acute infection, afebrile with normal sedimentation rate. Some of the children were admitted to the hospital for social reasons and some had a history of epilepsy but without any convulsions during their stay in the

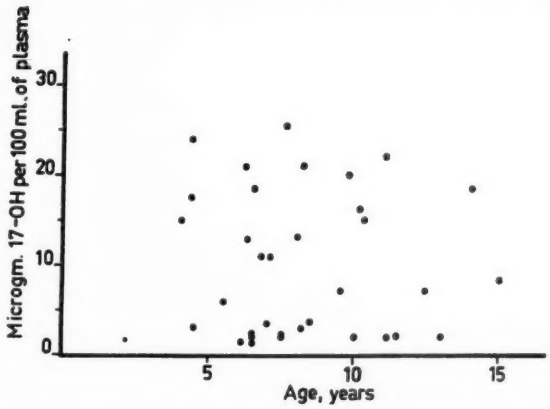

Fig. 1. Correlation between the plasma levels of 17-hydroxycorticosteroids and age of 34 normal children.

hospital. All the children were considered to be in a good state and normally developed. In 17 cases the skeletal age was determined and found to be in good correlation with their chronological age. Most of the children were between 5 and 10 years old (Figs. 1 and 2). The blood samples were taken on the same day as the urine was collected.

Results

As seen from Figure 1 the plasma levels of 17-hydroxycorticosteroids varied considerably between 2 and 26 μg per 100 ml of plasma and with an average value of 9.5 ± 1.41 μg. No correlation to age and sex could be established. The 17-ketosteroids showed the normal increase with age, reported earlier by many investigators (Fig. 2). It is evident from Figures 1 and 2 that no correlation exists between the plasma levels of 17-hydroxycorticosteroids and the urinary excretion of 17-ketosteroids.

Discussion

The results obtained in this investigation are in good agreement with the earlier reports of the plasma levels of 17-hydroxycorticosteroids in normal children. ELY *et al.* found in 26 children a mean value of 10.0 μg per 100 ml of plasma and KLEIN *et al.* reported in 41 "children and adults" a mean value of 13 μg per 100 ml of plasma. The wide variation found in this study was also reported by these authors.

In an earlier report the average plasma level of 17-hydroxycorticosteroids of 16 adult patients in the hospital was found to be 8.5 ± 1.40 μg per 100 ml of plasma (GEMZELL & FRANKSSON). In comparison to the average

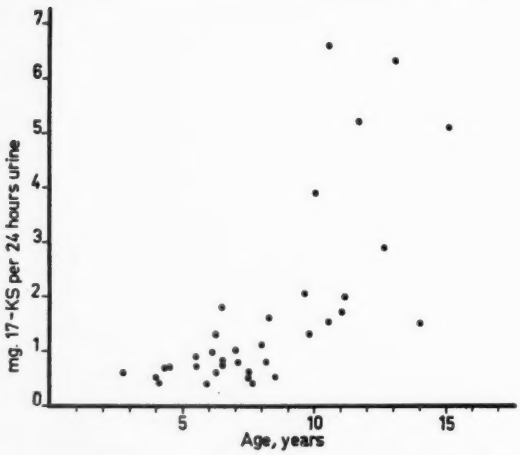

Fig. 2. Correlation between the urinary excretion of 17-ketosteroids and age of 36 normal children.

plasma level of the 34 children in this study (9.5 ± 1.41) there seems to be no significant difference between children and adults.

According to GEMZELL & FRANKSSON the level of 17-hydroxycorticosteroids varies during a 24 hours period with a maximum level in the morning and minimum level early at night. It is not likely that the distribution observed in this study was due to diurnal variations as the blood samples were taken at the same time in the morning in practically all the children.

In children with miscellaneous disorders high as well as low plasma levels of 17-hydroxycorticosteroids are reported (ELY *et al.*). According to KLEIN *et al.* the plasma levels of 17-hydroxycorticosteroids are significantly higher in children with acute meningitis than in normal children. The high values found in this study could not be correlated to any disease or to any known stress effect on any of the children.

In the present investigation a comparison of the plasma levels of 17-hydroxycorticosteroids and the urinary excretion of 17-ketosteroids has been made. Following surgical operation the urinary 17-ketosteroids increase together with the plasma levels of 17-hydroxycorticosteroids but the increase is very moderate compared to the increase of the plasma steroids (FRANKSSON & GEMZELL). This may be due to the fact that in adults only a small part of the 17-hydroxycorticosteroids are excreted as 17-ketosteroids (GEMZELL, BIRKE, HELLSTRÖM, FRANKSSON & PLANTIN). As the results of this study have shown, no correlation could be established in children between the plasma levels of 17-hydroxycorticosteroids and urinary excretion

of 17-ketosteroids. A correlation might have been expected in children as the 17-ketosteroids originate from the adrenals only and not from both adrenals and testis as in adults.

In demonstrating adrenal cortical activity, single determinations of 17-hydroxycorticosteroids are of little significance. Repeated determinations, especially after stimulation with ACTH, are preferable. Unfortunately, with small children the size of the blood samples makes duplicate determinations difficult.

Summary

The plasma levels of 17-hydroxycorticosteroids were studied in 34 children without evident disease. The results obtained are in good agreement with those previously reported by others.

The limited value of a single estimation of the plasma level of 17-hydroxycorticosteroids for evaluation of adrenal cortical activity is discussed.

A comparison between the urinary excretion of 17-ketosteroids and the plasma level of 17-hydroxycorticosteroids was made but no correlation could be demonstrated.

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Kronprinsessan Lovisas
Barnsjukhus
Stockholm

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From the Maternity Clinic I (Head: Prof. E. JERLOV) and the Maternity Clinic II (Head: Prof. H. FREDRIKSON) at Sahlgren's Hospital and from the Pediatric Clinic, The Children's Hospital, Gothenburg (Head; Prof. Y. ÅKERRÉN)

The Frequency of Congenital Toxoplasmosis and Some Viewpoints on the Diagnosis

by SVANTE C:SON HOLMDAHL *and* KURT HOLMDAHL

Congenital toxoplasmosis is a rare disease. The diagnosis therefore may seem to be of little practical importance. However, some of the most characteristic symptoms of this illness, convulsions, signs of encephalitis and hydrocephalus are common symptoms in other diseases. Therefore, the problem of excluding toxoplasmosis arises. The frequent occurrence of passively transferred antibodies against toxoplasma, demonstrable by titration, is of considerable practical importance in the diagnosis of this disease.

Investigations concerning the diagnosis and frequency of congenital toxoplasmosis have been published by, inter alia, SABIN & FELDMAN, SABIN *et al.*, BAMATTER, THALHAMMER, BUHN *et al.*, GARD *et al.* and S. HOLMDAHL. The most important results of the above investigations pertinent to this report can be summarized as follows:

1. Infection by toxoplasma produces an immunity demonstrable by the occurrence of antibodies in the blood. The two tests which are considered most reliable are the dye-test (DT) and the complement fixation test (CT). The antibodies demonstrable by DT apparently pass the placental barrier without difficulty and produce a passive immunization of the foetus. This is also true of antibodies determined by the CT, but to a lesser extent.

2. Antibodies against toxoplasma occur in 50 per cent of females in the fertile age. This also seems to be true in most West-European countries.

3. The children of these immunized females have an antibody titer at birth corresponding to that of the mother. The titer then, as a rule, drops to 0-values during the 4–6 first months of life. By the age of 4 months, the titer has usually dropped below 1:250. As these children do not show any clinical symptoms and have a rapidly falling titer, they are regarded as passively immunized.

4. In children who show clinical symptoms of congenital toxoplasmosis, the antibody titer remains elevated or may increase during the first several months of life. The mothers of these children always have a high titer shortly after parturition.

5. Even in fully developed congenital toxoplasmosis (the tetrad of chorioretinopathy, cerebral calcifications, hydrocephalus or microcephalus and psychomotor disturbances) the clinical symptoms alone do not prove that a toxoplasma infection is present. Usually the diagnosis can be determined serologically in 80–90 per cent. In many cases one or more features of the disease are missing. At times the only sign of congenital toxoplasmosis is an unilateral chorioretinitis (6). Neither is the pathologic-anatomic picture pathognomonic in all cases. The microbes are infrequently

demonstrable intravitally. With the aid of the serological methods, it is possible in most cases to establish the diagnosis. In less typical clinical or pathologic-anatomic pictures and in incomplete serological examinations the diagnosis can be difficult or impossible.

6. The frequency of congenital toxoplasmosis is considered low. However, hardly any reliable figures on incidence are available.

7. The cutaneous test is of little diagnostic value. Proven cases of congenital toxoplasmosis sometimes give negative skin reactions.[1]

It is usually possible to determine whether the antibodies present are due to active infection or passive immunization on the basis of repeated serological studies. Considerable diagnostic difficulties arise, however, if only single values are obtained shortly after birth. A negative test for CT combined with a high titer of DT in a newborn infant associated with a high titer of both antibodies in the mother's serum is considered proof of a recent and currently active congenital toxoplasma infection in the infant (10). In the cases where for some reason, e.g. death, not blood from the child has been obtained, diagnostic difficulties also arise. It has been pointed out (10) that a high DT titer in the mother does not prove that the child has had toxoplasmosis, but a negative or low titer in the mother within 3 years after delivery indicates that the child was not infected.

This paper is intended to elucidate the following points: (1) The frequency of passively immunized newborn infants and the course of their antibody curve. (2) The frequency of active toxoplasmosis in newborn infants and the course of their antibody curve, and (3) the reliability of performing a serological examination on the mother only, in order to throw light upon the diagnosis of uncertain cases where toxoplasmosis is suspected.

Material and Methods

The obstetrical material which is the basis of this examination has been presented previously in another connection (7). Therefore only a review of that report will be given. In Gothenburg during 1948–51, 23,260 children were born alive at the Maternity Clinics. They composed more than 95 per cent of the total number of children born in the city. Gothenburg is an industrial town and seaport with approximately 400,000 inhabitants.

Among the healthy mothers of the children born during these years, 415 were selected at random and examined by the DT titer. In approximately 50 per cent of the mothers, antibody titers between 1:10–1:8,000 were demonstrated. Approximately the same percentage was obtained in mothers who had various disturbances during pregnancy and delivery.

[1] The question as to the specificity of the toxoplasma-modifying antibodies demonstrated by the dye-test has been discussed by AVAD (The diagnosis of toxoplasmosis: Lack of specificity of Sabin-Feldman dye test. Lancet *267:* 1954, 1055). We will not discuss the problem, but call attention to the fact that this question does not influence the clinical aspects presented in this paper.

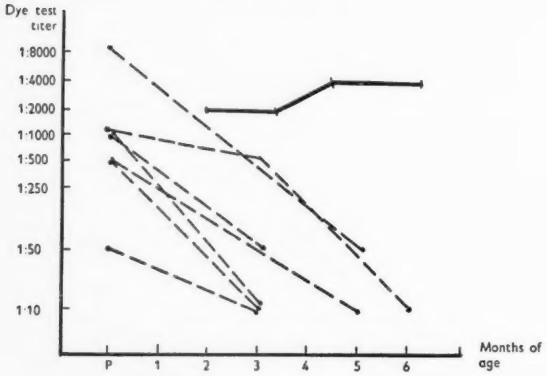

Fig. 1. Antibody titer in a child with congenital toxoplasmosis ——— and in 7 children with probable passive immunization – – – –. (In five of these children the titer at birth has been determined to correspond to the titer of the mother at delivery.)

Repeated testing until the time of delivery was done in 270 of the women. In 10 of them a DT titer $\geqq$ 1:250 was found at some time. According to the prevalent opinion such a high titer is indicative of a recent toxoplasma infection. Judging from the serological findings, one of these females became infected with toxoplasma during the second trimester of her pregnancy. The infants born of these 10 women who had high titers were studied with regard to clinical symptoms of toxoplasmosis in all and with regard to the course of the DT titer graph in 7 infants (Fig. 1). Clinical symptoms of toxoplasmosis were present in none. In two cases the blood from the umbilical cord was examined and showed a titer identical with that in the mother's blood. In the remaining five cases the titer of the child at birth has been tabulated (Fig. 1) and corresponds to the titer of the mother on the same occasion. The titer of these children had dropped to low values at the age of 3–6 months. One of these infants who was obviously passively immunized, still had a titer of 1:500 at the age of three months.

In Fig. 2 are given, inter alia, the serological values of the mothers of the seven children who were considered to have been passively immunized. Three of the mothers showed an unchanged or slightly higher titer when tested 3–5 months after parturition. Four of the mothers showed a decided drop in titer within 4–5 months after parturition.

All children born during 1948–51 at the Maternity Clinics were examined at birth and again at the age of one week by a pediatrician. All dead children were subjected to autopsy. Furthermore almost all children were followed up by a pediatrician during the first year of life and, in many cases, during the subsequent few years. It is likely that children with more obvious symp-

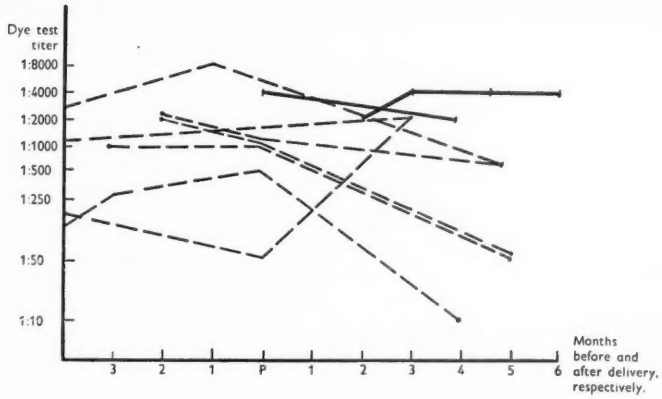

Fig. 2. Antibody titer in 2 mothers of children with congenital toxoplasmosis ———, and in 7 mothers with high titer values whose children are probably not infected wit toxoplasma – – – –.

toms were admitted to what is the only Children's Hospital of the city or to the Eye Department. At these clinics children having symptoms of toxoplasmosis have been subjected to the ordinary serological examinations. Of the children born during the time mentioned, so far (October 1954) two definite cases of congenital toxoplasmosis have been found. In another congenital toxoplasma infection may have been present. The cases were as follows:

Case 1.—Mother, Para III. Previous children healthy, age 13 and 6 years. The DT titer of the son, aged 6, is now negative. During the last months of pregnancy she had much throat trouble and was bed-ridden for two days during the last month due to sore throat with fever. During the last month of pregnancy she has been in contact with some baby birds, which died in her home after a few days. Length of pregnancy 30 weeks. Parturition normal. Birth weight 1,370 g. The child was highly asphyxiated at birth. Enlarged liver and spleen. Died at approx. three hours of age. Autopsy showed multiple foci of necrotic brain tissue. Microscopic examination revealed widespread necrosis with substance with the same staining properties as calcium. In some sections pseudocysts and microorganisms resembling toxoplasma were seen. The DT titer of the mother at parturition was 4,000 and 4 months later was 2,000 (Fig. 2).

Case 2.—Mother, Para I. The pregnancy was uneventful and parturition was normal. Birth weight 3,400 g. The head was somewhat large (38 cm). Shortly after the birth it was observed that the eyes were remarkable slit-like, especially the right. The anterior fontanel was unusually large. On follow-up examination at the Children Welfare Centre at the age of 1–2 months, the infant was admitted to the Children's Hospital. The size of the head was then 44.5 cm. The spleen was somewhat enlarged on palpation. Ophtalmoscopic examination revealed bilateral microophthalmus, signs of healed (?) uveitis and cataract in the right eye, and central and peripheral healed retinochorioditis in the left eye. There were arched intracranial calcifications bilaterally.

Cerebrospinal fluid obtained on puncture of the ventricle showed positive albumin reactions without an increase in cells. Attempts to isolate microbes were negative. The serological findings are seen in Fig. 1. Ventriculography at the age of five months revealed stenosis of the aqueduct with marked hydrocephalus. The child is 4 years old at present (October 1954). He is almost blind, the head size is 65 cm and his intelligence is decidedly low. The DT titer is 1:500. This is a classical case where the serological examination ensures the diagnosis.

Case 3.—Mother, Para I. Pregnancy and parturition were normal. The early development of the child was normal and has been healthy. Strabismus of the left eye was observed. An eye specialist was consulted at the age of 2. At this examination an uncertain fixation of the left eye was noted. There was a large central atrophic pigmentation of the left eye and in addition scattered peripheral foci. The right eye was normal. During hospitalization suspect spasms in the legs without loss of consciousness were observed on one occasion. No intracranial calcifications were demonstrated. The head size was normal for age. The C.S.F. was normal. Attempts to isolate toxoplasma from the fluid were negative. The DT titer was positive in dilution of 1:50 in both the mother and child. In this case diagnosis of toxoplasmosis could not be considered definite even if a positive titer at this age is strongly suggestive.

Discussion

As mentioned previously, approximately 50 per cent of newborn infants have antibodies against toxoplasma, most frequently as a sign of passive immunization. Of 270 pregnant women selected at random, 3.7 per cent had a DT titer of $\geqq$ 1:250. In accordance with this there ought to be approximately 800 newborn infants with such a high titer in the entire group under study. At the same time, there were only two cases with a definite congenital toxoplamsa infection in the whole material. This confirms the results of other studies (9, 10) that a definite diagnosis cannot be made on the preservation of a high DT titer in the newborn period. When by repeated tests it is demonstrated that the titer has remained high and unchanged or shows increasing values it is possible to establish a definite diagnosis of congenital toxoplasmosis. This is evident in Fig. 1. This investigation also confirms earlier observations that a toxoplasma infection recently acquired by the mother (cf. our case who probably became infected during pregnancy) ought not to mean a congenital toxoplasma infection in the child.

The longer after parturition a high titer ($\geqq$1:250) persists the more will it support the diagnosis. However, one can hardly state, as did SABIN *et al.*, that "when the dye test titer is 1:256 or more in both mother and child, provided the child is over 4 months of age" the diagnosis congenital toxoplasmosis is ensured. As seen in Fig. 1 an apparently passively immunized child can also show a titer of between 1:500 and 1:1000 at almost 4 months of age.

The frequency of congenital toxoplasmosis obtained in this study is no doubt too low. It is probable that some cases of chorioretinitis, as well as

cases which have not yet developed convulsions or other clinical symptoms of toxoplasmosis, have not been detected. It is also possible that some of the cases which have occurred have not come to our knowledge. Although, as far as we know, no definite cases of sub-clinical congenital toxoplasma infections have been described, there is none the less this possibility.

Due to the relatively long period which has elapsed since the birth of these children, and considering our facilities for observation of the entire group, it is justifiable to assume that the frequency obtained reliably reflects the occurrence of clinically more important congenital toxoplasmosis within a large group of children up to the ages of 3–6 years. The frequency is 1–2:10,000. Despite thorough examinations of all the stillborn children during the same period of time, no additional case of toxoplasmosis was noted (S. HOLMDAHL).

We have had no experience in diagnosis of active toxoplasmosis by determining both DT and CT in mother and child on single blood tests. We intend to investigate its value.

As has been mentioned, difficulties arise at times due to the fact that serum cannot be obtained from the infant for various reasons. Is there then no possibility of establishing the diagnosis by examination of the mother's blood only? SABIN *et al.* observed in children with congenital toxoplasmosis and in their mothers that the DT titer dropped to values below 1:256 only after one to several years. They state that a low titer or a negative titer in these mothers within three years after parturition excludes toxoplasmosis. On the other hand some authors (e.g. GARD *et al.*) have found low titer values within shorter intervals after parturition. The mother of the definite case observed by GARD *et al.* had a titer of 1:50 after delivery within 31 months. In definite toxoplasma infections at times the titer falls below 1:250 within a year (GARD). Fig. 2 also shows a comparison between the titers of mothers with infected children, and those with passively immunized children. A maternal DT titer below 1:250 within four months after parturition can almost with certainty exclude a toxoplasma infection in the child, even if the titer at birth was above this value. In addition, if the titer is low during the first three months after birth, a toxoplasma infection is very unlikely. Since approximately 90 per cent of the females have such a low titer (in our material 96.2 per cent of 270 females) it is possible to exclude a toxoplasma infection in their children by testing only the mother's blood.

If the mother, however, has a high titer which does not fall below 1:250 within 4–6 months, it is not possible to exclude a toxoplasma infection in the child. An unchanged or even increasing titer (see Fig. 2) as previously mentioned in the mother may be associated with a child without clinical

symptoms of toxoplasmosis and with a titer curve consistent with passive immunization. In these cases, comprising approx. 10 % of the total in which there are symptoms of toxoplasmosis, a serological examination of the child should be made if possible.

Conclusions and Summary

1. One half of all newborn infants can be expected to have antibodies against toxoplasma with DT titers between 1:10 and 1:8,000. In the majority of cases, this titer is a passive immunization acquired during the intrauterine life. In the passively immunized children, the antibody titer falls to values $< 1{:}250$ during the first six months of life. At the age of 3–4 months some children may have a titer of 1:500 and in all probability a sign of a passive immunization.

2. During a four-year period it was possible among 23,260 children born alive, who had been under observation up to the age of 3–6 years, to establish two definite and one probable cases of congenital toxoplasmosis. The frequency obtained (1–2:10,000) is probably too low but is a rather reliable incidence for the occurrence of clinically significant congenital toxoplasmosis in the population of a city in Sweden. Of the two definite cases of toxoplasmosis one survived the neonatal period and had a persistent high antibody titer for many years, in contrast to the children who were passively immunized.

3. If only blood from the mother is available an active toxoplasmosis in the newborn child can be excluded in most instances if the titer of the mother at parturition or during the first 4–6 months afterwards has a low DT titer (less than 1:250). This can be expected in about 90 per cent of all mothers. These mothers frequently have a rather high titer at parturition (Fig. 2). Inversely, if the mother has a persistently high or increasing DT titer ($\geqq 1{:}250$) 4–6 months after parturition, there is the possibility that the child may be infected with toxoplasma. A clinical and serological examination with special regard to the toxoplasmosis should be made in these cases.

La fréquence de la toxoplasmose congénitale et certains aspects de son diagnostic.

La moitié de tous les nouveau-nés possède des anticorps contre la toxoplasmose, le titre variant de 1:10 à 1:8000, ceci signifiant une immunisation passive pendant la vie intra-utérine. Pendant les six premiers mois le titre d'anticorps est 0 ou inférieur à 1:250; même à l'âge de 3–4 mois certains nourrissons ont un titre de 1:500, ceci étant très probablement un symptôme d'une immunisation passive. L'auteur a trouvé deux cas certains et un cas incertain de toxoplasmose congénitale parmi 23 260 nouveau-nés. Un de ces nourrissons a survécu la période néonatale et le titre des anticorps est resté pendant les six premiers mois élevé. Si la mère a un titre peu élevé (moins de 1:250) au moment de l'accouchement ou pendant les 4–6 premiers mois suivants, le nourrisson peut être considéré comme exempt de toxoplasmose (environ 90 % des mères). Si la mère présente un tire continuellement élevé ou s'élevant (égal ou supérieur à 1:250) après 4–6 mois le nourrisson est possiblement atteint de toxoplasmose.

Die Häufigkeit von kongenitaler Toxoplasmose und einige Gesichtspunkte zu ihrer Diagnose.

Die Hälfte aller Neugeborenen besitzt Antikörper gegen Toxoplasmose mit Titerwerten zwischen 1:10 und 1:8000 als Ausdruck einer passiven Immunisierung während des intrauterinen Lebens. Während der ersten 6 Lebensmonate fällt der Antikörper-

titer auf Null oder auf Werte, die 1:250 nicht überschreiten. Noch während eines Alters von 3–4 Monaten besitzen einige Kinder einen Titerwert von 1:500, aller Wahrscheinlichkeit nach ein Zeichen einer passiven Immunisierung. Unter 23260 neugeborenen lebenden Säuglingen wurden 2 sichere und 1 unsicherer Fall von kongenitaler Toxoplasmose gefunden. Einer dieser Säuglinge überlebte die neonatale Periode und wies einen persistierenden hohen Antikörpertiter während der ersten 6 Monate auf. Wenn die Mutter während der Geburt oder den darauffolgenden 4–6 Monaten einen niedrigen Titer zeigt (weniger als 1:250), kann der Säugling als frei von Toxoplasmose betrachtet werden (ungefähr 90 % aller Mütter). Sollte die Mutter einen dauernd hohen oder steigenden Titer (1:250 oder darüber) 4–6 Monate nach der Geburt besitzen, so ist der Säugling möglicherweise mit Toxoplasmose angesteckt.

Frecuencia de toxoplasmosis congénita. Consideraciones diagnósticas.

La mitad de los recién nacidos presentan anticuerpos contra el toxoplasma cuyo título varía entre 1:10 y 1:8000, como signo de inmunización pasiva adquirida durante la vida intrauterina. A los 3–4 meses algunos niños posseen un título de 1:1500 que cae al cabo de seis meses a valores entre 1:250 y 0. En 23260 niños vivos se encontraron 2 casos positivos y uno incierto de toxoplasmosis congénita. Uno de estos sobrevivió al período neonatal mostrando un alto título de anticuerpos durante los primeros 6 meses. Si la madre presenta en el momento del parto o durante los primeros 4–6 meses un bajo título de anticuerpos (menos de 1:250), puede considerarse al hijo libre de toxoplasmosis. Por el contrario, si esta presenta una cifra persistentemente alta (igual o más de 1:250) o en aumento, possiblemente el niño esté infectado.

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The Children's Hospital
Gothenburg, Sweden

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From the Pediatric Clinic of the Children's Hospital, Gothenburg
(Head: Prof. Y. Åkerrén)

Milk Drip via an Indwelling Naso-Gastric Rubber Tube for Feeding Premature Infants

by KURT HOLMDAHL

The usual method of feeding premature infants by inserting a tube into the stomach several times a day has certain disadvantages. Attacks of asphyxia are frequently associated with this technique. The risk of vomiting increases with large infrequent feedings, and it is often difficult to nourish these infants with frequent small feedings. Moreover, experienced personnel is required to insert the tube to administer the feedings. In order to decrease these disadvantages, the method of an indwelling naso-gastric tube has been used during recent years.

Introduction

In 1951 Royce *et al.* and Andrews & Traisman published their experiences in feeding premature and older infants respectively with an indwelling naso-gastric plastic tube. Good results have also been reported by Wagner *et al.* (1952), by Holmdahl (1953), and recently by Kauhtio (1954). Since February 1952 Kauhtio has used the method on 73 prematures.

Polyethylene or plastic tubes have been used because of minimal irritation to the tissue. Despite this, a change of the catheter is often recommended after a relatively short period (1–2 weeks). The technique of feeding is simple. Milk or other suitabel nutrient is given either at frequent intervals or by a continuous drip into the nasogastric tube.

Vomiting and attacks of cyanosis are not uncommon to both techniques, however. Vomiting is considered to be less when an indwelling tube is used. There are no figures proving the value of the new method because of the difficulty in obtaining satisfactory control material. The value of the method is considered to be due to the reduced necessity of handling the child, the decreased risk of aspiration and vomiting, and the time-saving factor. Crosse believes that the children often become restless by this treatment and that there is considerable risk of damage to the mucous membrane of the nose. She considers that the method should be reserved for premature infants weighing less than 1,000 g. Most investigators have reported insignificant irritation and bleeding of the mucous membrane of the nose. In addition, perforation of the stomach has been reported (Kunz). Kunz and Royce have suggested methods of preparing the tip of the tube to prevent trauma to the tissues.

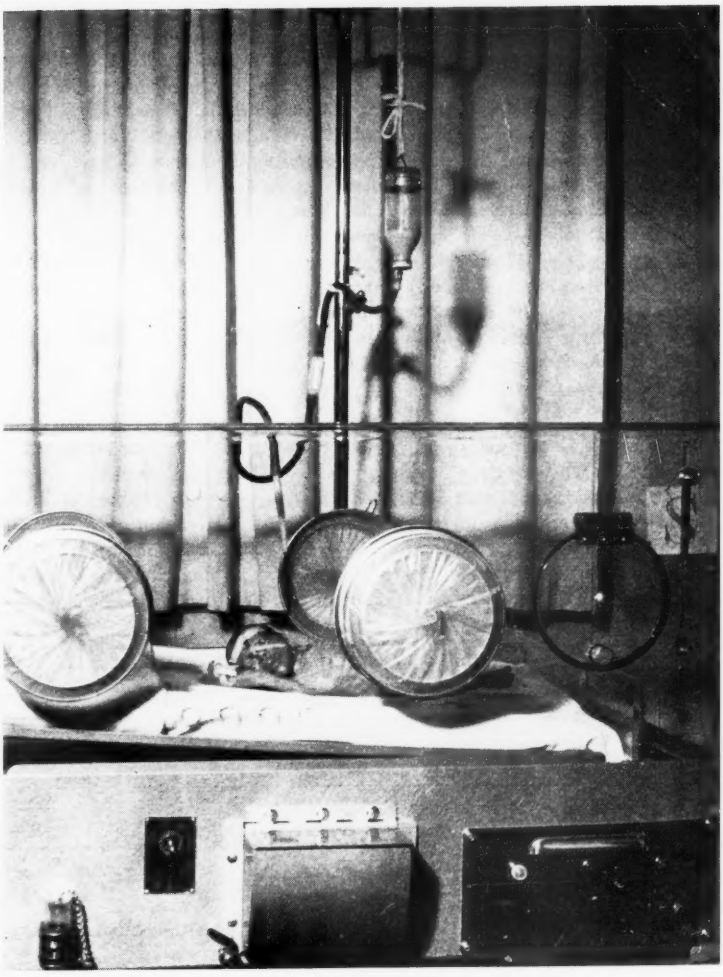

Fig. 1.

Since July 1952 we have been using a modified method. An ordinary soft rubber catheter has been used which, owing to its flexibility and elasticity probably does not involve the risk of perforation. The milk is supplied routinely in a continuous drip in order to prevent the stomach from expanding excessively, which increases the risk of vomiting and in addition may have an undesirable effect on respiration and circulation. It is the purpose of this report to survey our experience with naso-gastric feeding through an indwelling tube.

Technique

The apparatus is shown in Fig. 1. The tube is a soft Nélaton No 6. The volume of the bottle is about 100 ml. There are two hypodermic needles in the rubber cork. One of these is to secure the supply of air to the bottle and debouches into a glass tube inserted into the cork, which extends above the level of the liquid in the bottle. The approximate distance from the nose to the stomach is measured. This length of a sterile tube is inserted through the nose into the stomach. The free end is attached with strips of adhesive plaster. Then the drip is connected. The calculated amount of nutrient is divided into 3–4 portions and supplied at a dripping rate of 5–10 drops per minute. Every meal lasts about two hours. When the meal is terminated the indwelling tube is flushed with water. A small wooden stick keeps the tube closed between the meals. As a rule the tube is left in the same nostril for 2–3 weeks. The drip apparatus is sterilized after use. Complete apparatuses for milk drip to prematures are manufactured by KIFA, Stockholm.

Case Material

We have used this method on all prematures weighing less than 1,500 g at birth and other infants who have required tube feeding. A total of 72 premature infants, 46 of whom weighed less than 1,500 g, have been fed this way (Table 1). Continuous nourishment was generally begun twelve hours after birth, and continued until another type of feeding could be used. Spoon feeding and rubber nipple feeding can be started later on without difficulty while the tube remains. The duration of the continuous feeding varied between one week to several months. The total number of tube days is at present approx. 1,500.

TABLE 1

Number of premature infants fed on milk drip. Deaths in brackets.

≤ 1,000 g Birth weight	1,010–1,500 g	1,510–2,000 g	2,010–2,500 g	Total
9 (4)	37 (4)	16 (1)	10	72 (9)

Results

To estimate the value of this method, a comparison with the results of intermittent feeding used previously was possible. During the years 1948–1950 the intermittent oro-gastric technique was used, and during 1952–1954 the indwelling naso-gastric technique was used. In Table 2 the occurrence of emesis and attacks of cyanosis in both techniques is tabulated. It is seen that the frequency of emesis was slightly less with the new method. However, the attacks of cyanosis occurred in approximately the same frequency. A determination of the severity of the attacks of cyanosis was desirable, but proved too difficult to do accurately. One infant died of aspiration with fatal asphyxia. Table 3 shows that the death-rate decreased generally, which was especially remarkable in the weight group below 1,500 g.

TABLE 2

Comparison between occurrence of vomiting and attacks of cyanosis in premature infants (birth weight ≤ 1,500 g) during nutrition with milk drip through indwelling naso-gastric tube and during intermittent oro-gastric tube-feed.

	Number of tube days	Vomiting	Tube days per attack of vomiting	Attack of cyanosis	Tube days per attack of cyanosis
Naso-gastric tube feed, 23 cases	473	37	12.9	48	9.9
Oro-gastric tube feed, 23 cases	367	55	6.7	38	9.7

TABLE 3

Distribution of live births by weight groups and neonatal mortality rate within 4 weeks after birth.

Birth weight in g	Gothenburg 1948–1950			Gothenburg 1952–1954		
	Number of cases	%	Mortality within 4 weeks, %	Number of cases	%	Mortality within 4 weeks, %
≤ 1,000	40	5.9	97.5	30	6.7	83.3
1,010–1,250	74	10.9	60.8	23 + 29 = 52	11.6	47.8 + 34.5 = 40.3
1,260–1,500			73 %			56 %
1,510–2,000	147	21.7	8.8	91	20.3	8.8
2,010–2,500	416	61.4	5.8	275	61.4	1.5
Total	677	100	18.1	448	100	12.9

However, the death-rate decreased considerably in the 2,010–2,500 g weight group where tube feeding only rarely occurred. In Table 4 is seen that the late-mortality, i.e. the death-rate between 48 hours and four weeks after birth, is lower than previously. It is important to mention that during the two years that this tube feeding method has been used, five children weighing less than 1,000 g have survived; while during the preceding 14 years, only two children in this weight group survived. The tube feeding has, as a rule, not involved any difficulties. Rarely the larger infants, (more than 2,000 g) have shown signs of restlessness or inconvenience. These infants, at times, have managed to pull out the tube by moving their arms. This has been checked by applying adhesive plaster along the root of the nose and the forehead (see Fig. 1), and by dressing the child in a sleeveless shirt. Slight nasal irritation has occurred, in some instances necessitating a change-over to another feeding method.

TABLE 4

Distribution of neonatal deaths according to age at death and the mortality risk after the lapse of 48 hours.

	Premature infants born alive	Deaths within 48 hours	%	Surviving after 48 hours	Deaths within 4 weeks	%
Gothenburg 1948–1950	677	101	14.9	576	19	3.3
Gothenburg 1953–1954	448	53	11.8	395	5	1.3

Discussion

Even if the previous comparisons in figures between the earlier used tube feeding method and the present method seem to point to the advantage of the latter method, no definite conclusions can be drawn. The differences are so slight that they may not be significant, and also the control material is not quite equivalent.

When calculating both the morbidity and the mortality the control material belongs to the nearest preceding period. Considering the new treatment principles, which have been used on prematures, the various methods of feeding are not the only things which separate the two groups.

It is, however, justifiable to say that there is no impairment of the results. The only death from aspiration mentioned earlier occurred in a premature infant with a low birth weight. Such cases happen now and then with all types of feeding methods on premature infants and this case, therefore, is of no great importance in judging the value of the method.

Since the treatment has not been detrimental this technique is recommended as a routine method for premature feeding. The practical advantages, especially the reduced work and the smaller demands of less qualified personnel, are a sufficient motive. The method of continuous supply of nourishment by drip employed by the author is more preferable from the practical point of view than the previously used method of indwelling tube and frequent small feedings. The following advantages are attained: (1) Reduced personnel. (2) Less disturbance to the children. (3) Constancy of incubator oxygen, as the bottle can be changed outside the incubator; this may be important in preventing retrolental fibroplasia. (4) Greater quantity of nutrient without danger of gastric distension. In fact, approximately 25–50 per cent more nourishment per time unit can be supplied by the continuous drip technique. (5) A rubber catheter can be used without inconvenience. We have no experience of such a catheter damaging the mucous membranes. The rubber catheter is superior to the polyethylene

because of its softness, elasticity and tenableness when sterilizing etc. The modifications recommended to reduce the risk of using polyethylene tubes are, therefore, superfluous.

Summary

A modification of naso-gastric feeding of prematures and other infants utilizing an indwelling rubber catheter, and nutrient administration by continuous drip is presented. Successful use of this technique has been demonstrated in 72 premature infants. This method is more advantageous than previous feeding techniques because the frequency of vomiting is decreased, the infant is disturbed less and may be fed without removal from an incubator, the administration of nutrient may be given by less skilled assistants in less time, irritation to the mucous membranes is minimal, greater quantities of nutrient may be given during a 24-hour period, and statistical comparison with previous techniques suggests that more infants weighing less than 1,500 g have survived. A review of the literature is presented.

Introduction d'un tube naso-gastrique en caoutchouc pour l'alimentation de nourrissons prématurés.

Les aliments ont été donnés en goutte à goutte lent par une sonde à demeure en caoutchouc (Nélaton N° 6) pendant une longue période. Cette méthode a été employée depuis 1952 par routine chaque fois que l'alimentation par sonde était nécessaire. On en a fait usage chez 72 nourrissons prématurés pendant un total de 1500 journées d'alimentation à la sonde. Certains enfants ont été alimentés à la sonde jusqu'à l'âge de 2–3 mois. Grâce à sa mollesse, son élasticité et sa résistance pendant la stérilisation le caoutchouc est pour cet usage supérieur au polyethylene.

Naso-gastrischer Dauer-Gummikatheter zur Ernährung prämaturer Säuglinge.

Die Nahrung wurde durch einen Gummikatheter (Nelaton Nr. 6) in Form langsamen Dauertropfs während einer langen Periode zugeführt. Die Methode wurde seit 1952 routinemässig durchgeführt, sobald Sondenernährung benötigt wurde. Sie wurde bei 72 prämaturen Säuglingen während einer totalen Anzahl von 1500 Sondentagen angewandt. Einige Kinder wurden bis zu einem Alter von 2–3 Monaten mit Hilfe der Sonde gefüttert. Mit Hinblick auf seine Weichheit, Elastizität und Widerstandskraft in Bezug auf Sterilisierung ist Gummi dem Polyaethylen für diese Anwendung überlegen.

Sonda naso-gástrica permanente de caucho para alimentación del prematuro.

Los alimentos han sido administrados por medio de un catéter de caucho (Nelaton N. 7) en forma de perfusión continua durante largos períodos. Este ha sido el método de rutina desde 1952 cada vez que un prematuro ha requerido alimentación por sonda. Ha sido empleado en 72 niños con un total de 1.500 días -sonda. En algunos casos se usó este método hasta la edad de 2–3 meses. El tubo de caucho ha demostrado ser superior al de polyethylene por su elasticidad, blandura y resistencia a la esterilización.

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Children's Hospital
Gothenburg, Sweden

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A Field Study of Mental Subnormality in Children

by GILLIS HERLITZ and BJÖRN REDIN

The term "mental subnormality" is generally used to designate a condition of incomplete general development of the mental capacities. Much confusion prevails concerning the border line between this condition and the state which might be characterized as mentally normal. Besides this, the criteria of mental subnormality are vague and uncertain. Intelligence tests have a limited function in the diagnosis. Social, educational, temperamental and moral factors must also be taken into account, especially in the milder grades of the disturbance. All these factors contribute towards the difficulty in obtaining constant results and comparable figures.

Here, a mentally subnormal child is to be understood as one who because of a general mental retardation is unable to follow the ordinary instruction given in Swedish elementary schools or in the special classes of these in which a slightly modified instruction more suited to backward children is given. With this definition we have followed the Swedish tradition in this field and the new Swedish laws concerning the mentally retarded. Thus, the border line will be drawn at an intelligence level corresponding to that of about 10–11 years for adults (IQ about 65–70).

We carried out a census investigation of mentally subnormal children in the county of Östergötland, a predominantly rural district in the south of Sweden with a total population of 265,670, of which 40 per cent are living in the towns. The investigation was limited to 10 one-year classes, namely from 2–11 years. Half of this group fall below school age, the other half within school age.

The county, including its six towns, is divided into 59 districts, in each of which is a district nurse, who is usually well acquainted with the state of health of the children in the families in her district of some 4,500 persons. All of these nurses received questionnaires which they filled in, usually after consulting the provincial physician, and returned to us. In addition information was requested from all the 46 primary school boards, where registers are kept of all children of school age, from the 45 boards of childrens' welfare and the 155 parish offices (the clergymen of the parishes usually know the families in their parish well and keep a register of all

TABLE 1

Distribution of cases according to sex and age.

Age in years	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	Total
Girls	6	6	11	6	11	11	11	16	13	14	105
Boys	12	8	18	21	15	10	27	17	12	17	157
Total	18	14	29	27	26	21	38	33	25	31	262

mentally deficient persons). Answers were received from all these authorities except one parish office. All Child Welfare Centers in the towns also co-operated. The county has only one children's hospital and there all the records of in- and out-patients were perused. All institutions and schools for mentally subnormal children in the county have been checked, including the records of admitted, discharged and expected children, the majority of whom have been examined by us for this investigation. In those cases in which a child had been cared for in institutions outside the county, the desired information was received from there.

Once the names of the children were known, the factors to be analysed were searched for with the help of teachers and nurses, hospital records, personal investigations, etc., as far as possible in every individual case. The information of the state of health of the mother during pregnancy, delivery, weight at birth and state of health during the first week after birth was obtained from the hospitals where the children had been delivered. Of 213 children whose place of birth was known, 97.6 per cent had been born in hospitals.

Incidence.—The total number of cases discovered was 262. The children are classed according to sex and age in Table 1.

One might have expected the total number of children to be the same in the group above and the group below 7 years—the school age in Sweden—because the normal population in these age classes in our county shows this distribution; but 56.5 per cent of the present material were found to be above 7 years. This might be due to chance (diff. $= 6.5 \pm 3.06$ per cent), but it is, of course, more likely that mental subnormality is often not discovered or acknowledged until the children begin school. That the difference is not greater reflects to a certain extent the effectivity of the inventory.

At the time of the investigation, 51.0 ± 0.24 per cent of the total population in the ages 2–11 years in our county consisted of boys. As usual, in materials like the present, the boys predominated. This applies above all to the age classes below 7 years, where the frequency of boys was 64.9

TABLE 2

Clinical types.

Age in years	Boys			Girls			Both sexes			Both sexes
	2–6	7–11	2–11	2–6	7–11	2–11	2–6	7–11	2–11	7–11 per cent
Idiopathic oligophrenia.	38	44	82	12	35	47	50	79	129	53.4
Cerebral palsy	13	16	29	12	14	26	25	30	55	20.3
Mongolism	16	14	30	10	10	20	26	24	50	16.2
Epilepsy	6	8	14	3	4	7	9	12	21	8.1
Hydrocephalus	1	1	2	2	1	3	3	2	5	2.0
Cretinism	0	0	0	1	1	2	1	1	2	
Total	74	83	157	40	65	105	114	148	262	100.0

per cent as against an expected frequency of 51 per cent. The difference (13.9 $\pm$4.47 per cent) is statistically significant. This point will be referred to in a later section.

On December 31, 1953, there were 46,100 children in the age classes 2–11 years in the county of Östergötland, fairly evenly distributed among the 10 one-year classes. On the basis of the age group 7–11 years, which shows the highest frequency of backward children in the material (29.6 cases per year class of 4,600 children), the incidence of mental subnormality in our county will be 6.4 per 1,000 children in the age classes in question. For boys alone the figure will be 7.1 per 1,000, and for girls, 5.8 per 1,000. As usual in census investigations, the figures must be regarded as minimal values.

Clinical types.—Exclusion of the well characterized groups of cerebral palsy, mongolism, hydrocephalus and cretinism from the total material, will leave a large group of mental subnormality within which a further classification into distinct clinical types is more difficult. This latter group includes some children with epilepsy, possibly indicating a more flagrant anatomical damage to the brain. If the epileptic children are taken together as a separate clinical group, the remainder will consist of cases in which no special clinical symptoms or obvious etiological factors are available to justify a further clinical classification. These independent or primary cases, without apparent symptomatic or traumatic origin, represent about half of the total material. In the absence of anything better, we have termed the group idiopathic oligophrenia. It thus consists of both sporadic and hereditary cases.

The distribution of the clinical types is given in Table 2.

The various clinical types are represented by roughly the same number of cases above 7 years as below, with the exception of idiopathic oligophrenia, which shows a lower frequency in the age below 7 years. The girls seem to be practically entirely responsible for this low frequency. They stand for only 12 cases in the lower age group, as against 35 in the higher. Statistically, this may be due merely to chance, but it seems probable that, for some reason or other, idiopathic oligophrenia below school age is not so readily noticed or admitted in girls as it is in boys. At the beginning of school age there seems to be a relative numerical balance. At any rate, the above-mentioned general under-representation of children below 7 years of age in the total material is due mainly to the fact that a fair percentage of the girls with idiopathic oligophrenia in preschool age escaped detection.

Educability.—The term educability of mentally subnormal individuals is difficult to define. The general notion of the term, therefore, varies with different conventional concepts. Nevertheless, in practice, it is of great value to be able to draw certain limits distinguishing those children in whom a trial at teaching may possibly pay back, from the others. There are, then, primarily two types of educability that should be considered, namely, practical and theoretical.

A backward child must be regarded as practically educable if it can be taught to manage itself, to eat without help, to dress himself, and to go to the toilet, use a rake or other simple tools, to go small errands, to do simple chores, etc. The lower limit for these practically educable, as measured by ordinary intelligence tests, varies widely. In some cases some of the above-mentioned accomplishments can be taught and developed, even in children with very low intelligence quotients (about 25 and lower). It is therefore hardly possible to form even an approximate opinion of the practical educability of a backward child by the IQ alone. Here, of course, it must also be remembered that, for obvious reasons, the test must be less reliable the lower the patient is on the intelligence scale.

As far as theoretical educability is concerned, the situation is not quite so difficult. Theoretical educability is to be understood as an ability to learn how to use the symbols of arithmetic and the spoken sounds (figures and letters). The lower limit of this ability can, with fair accuracy for practical purposes, be drawn by means of the usual intelligence tests. It is generally accepted that this ability is almost always to be found in a child whose IQ exceeds 50, while a child below 40 will hardly ever be susceptible to this kind of education. Thus, in the estimation of the educability of the present material, an IQ of 45 was taken as an approximate limit between the theoretically educable and non-educable children. Naturally, this was

TABLE 3

Theoretically educable girls and boys above 7 years of age.

	Mongolism	Epilepsy	Cerebral palsy	Idiopathic oligophrenia	Total group
Educable?	3	0	1	9	13
Educable	0	5	10	55	70
Non-educable	21	7	19	15	65
Total	24	12	30	79	148
Non-educable in per cent of total	87.5	58.3	63.3	19.0	43.9

only a coarse gradation, but it is still more precise and useful than the corresponding gradation concerning the practical educability.

Since it is often a hazardous task to come to a definitive conclusion about the mental educability of backward pre-school children, we limited our investigation to the children above 7 years of age (Table 3). Most of them have attended special schools for mentally subnormal children. The results of these attempts at teaching confirmed the usefulness of the above-mentioned IQ limit.

Heredity.—Our information concerning this point is incomplete, especially with respect to the parents. In spite of this the following figures are given.

In the group of idiopathic oligophrenia (129 cases, of which 14 are registered as the only child) mental retardation in siblings is reported in 34 cases; they originate from a total of 24 families. Two of these families have 3 children each in the material, 6 families have 2, and 16 families have 1 child each in the material. In 16 cases of the same group, among which are 2 siblings, one of the parents is said to be mentally retarded; in 3 additional cases, 2 of which are siblings, both parents are mentally retarded.

Etiologic factors.—As mentioned, among the mentally subnormal children we find some clinical types which are, generally speaking, readily distinguishable from the others and which form circumscript units. In our material, this applies above all to cerebral palsy, mongolism, hydrocephalus and cretinism. For reasons given above, it might be possible to regard the epileptic children as such a group. The remaining cases, which are classed here as idiopathic oligophrenia, do not form a uniform group from an etiologic point of view, because they include both hereditary and sporadic cases. It is, above all, the latter that are of interest in the discussion of etiology.

It is known that injury to the brain in children is often due to complicated pregnancy and/or partus. Maternal disease, abnormal delivery and prematurity are regarded as the commonest causal factors. The hypoxaemic conditions in the newborn due to any of the three factors given above, or other factors, have often been blamed for the cerebral injury of spastic children. In order to determine to what extent these injurious factors are involved in the development of the sporadic idiopathic oligophrenias, we investigated the children of the present material for the occurrence of such injuries.

The idiopathic oligophrenia group consists of 129 cases. Mental retardation was reported in siblings and/or parents of 49 of these patients. The remaining 80 cases were classed by us as sporadic oligophrenia, although, of course, they might have included some cases in which actual hereditary factors did not come to our knowledge. In 71 of these 80 cases the children had been born in hospital and, therefore, complete information was available concerning the state of health of the mother during pregnancy, the course of delivery, the weight at birth, and the state of health of the children during the first week of life.

The records of 36 (50.7 per cent) of these 71 cases of sporadic oligophrenia showed either maternal disease during pregnancy (12 cases), abnormal parturition (15), prematurity (17), signs of cerebral injury during the first week of life (11) or combinations of these four (11). Prematurity was said to be present when the child weighed less than 2,500 g at birth. The criteria of potential injury are given in Tables 4—6.

In a control series (200 newborns selected at random from the corresponding years at the hospital, where most of the probands were born) potential injury, as judged by these criteria, was demonstrable in only 20 per cent. The difference (30.7 ± 6.58 per cent) is statistically significant.

For that part of the idiopathic oligophrenia group, where mental retardation was reported in the siblings or the parents, the corresponding figure was 24 per cent. The material here is small, but the difference between the percentages, 50.7 and 24, is larger than 2.5 times their mean error (26.7 ± 10.40 per cent) and is, therefore, statistically probable. The fact that sporadic idiopathic oligophrenia in our material might have included children with a hereditary disposition implies that, in reality, the difference between purely sporadic and the hereditary cases might have been still more marked.

Injurious factors of the type under discussion were demonstrated in 74 ± 6.2 per cent of those 50 children in the cerebral palsy group about whom complete information was available concerning pregnancy, birth and the first week of life. The corresponding figure for epileptics was 56.3 ± 12.4 per cent.

TABLE 4

Maternal disease during pregnancy.

	Number of cases
Placenta praevia	1
Hemorrhages mens. II	1
Nephropathy with hypertension	2
Hypertension, toxicosis	1
Rubella mens. III–IV	2
Syphilis II	1
Imminent abortion mens. II–III	1
Hypothyreosis	1
Attempted suicide mens. II (sedatives, loss of consciousness)	1
General anaesthetic mens. II (operation for appendicitis)	1
Total	12

TABLE 5

Abnormal partus.

	Number of cases
Forceps	2
Caesarian section	2
Breech delivery	6
Prolonged parturition (more than 36 hours	5
Total	15

TABLE 6

Signs of cerebral injury during first week of life.

	Number of csaes
Cyanosis, asphyxia	8
Convulsions	1
Rigidity	1
Distended fontanel, flaccidity, apathy	1
Total	11

Discussion

For several reasons it is difficult to compare investigations of the frequency of mental subnormality by various authors in different regions at different times. It is not only the differences between the chosen limits on the intelligence scale, and differences in the technical procedure adopted for collecting the material, that makes such comparison difficult. The varying age distribution in the material, the changing composition of the population and the percentage of people moving (if emigration is pronounced, the relative frequency of oligophrenia will increase, oligophrenics being more stationary), the possible character of an eugenic isolate of the region studied and several other factors make comparisons hazardous. Nevertheless, a short review is given below of the results of some—mainly Scandinavian—investigations.

KÄLLMARK, on the basis of information from parish offices, relief offices, etc., in a Swedish province (the county of Uppsala), gave an incidence of mental subnormality in the total population of 4.6 per 1,000. In a small population of 738 persons over 10 years of age on the Danish island Bornholm, STRÖMGREN found the frequency of idiots and imbeciles to be 12.2 per 1,000. KAILA found, among half a million persons in all ages in the rural districts of Finland, the frequency of idiots and imbeciles to be 4.4 per 1,000. For the ages 10–14, the figures were 12 per 1,000. SJÖGREN, in an investigation of some west Swedish islands, of altogether 9,000 inhabitants, found a frequency of idiots and severe imbeciles of 6.8 per 1,000. In the so-called Wood Report, LEWIS published the results of his extensive intelligence tests of representative groups of children in a district of 600,000 inhabitants in England. In the age classes 7–14 years he found the frequency of imbeciles and idiots to be 3.76 per 1,000 in towns, and 6.14 per 1,000 in the country.

In field investigations of this type it should be borne in mind that the highest relative frequency of mentally subnormal individuals in a population—except in the lowest age classes, is always to be expected in the age classes falling within school-age. During this age, intellectual selection is more stringent and more just than during any other period of life for the population in general, including age for military enlistment. Later in life, many of those who fall below standards at school choose an occupation in which their intellectual deficiency is no longer so readily detectable. The defect nevertheless persists and, therefore, in the calculation of the frequency of mental subnormality in a population it is advantageous to base conclusions on the figures obtained from investigations of school children, unless one is prepared to carry out the time-consuming and

reliable measurements of the intelligence of large groups of adults with an ever increasing heterogeneity. One must then also take into account the average expectation of life for the oligophrenics, which is given as 75—80 per cent of that of the normal population (SJÖGREN).

Half of the children in our series of sporadic idiopathic oligophrenia were found to have some potential injury sustained in association with the pregnancy of the mother, or at delivery, or to be of abnormally small weight at birth, or to have shown signs of cerebral injury during the first week of life. This is perhaps not surprising. As to the children with cerebral palsy, we know that such injuries are very common findings. In an unselected group of 83 children with cerebral palsy and consisting of both mentally normal and mentally abnormal children, HERLITZ & REDIN found corresponding injurious factors (pregnancy, partus and birth weight) in 66.3 per cent. Cerebral palsy is seen in children who have sustained injury to the motor centra in the brain. In those cases in which the spastic children became mentally subnormal, the mental centra, speaking schematically, were also involved. It must, therefore, be reasonable to suppose that there are also cases in which the injury involved only the mental centra, and then the symptoms should consist of intellectual deficiencies without central-motoric disturbance. It is these cases we believe to have identified in our group of sporadic idiopathic oligophrenia.

Our observations have led us to the conclusion that it is almost as often trauma sustained at delivery and similar causes that are responsible for sporadic idiopathic imbecility and idiocy as for cerebral palsy.

Summary

A description is given of a census investigation of imbecility and idiocy within a group of children comprising 10 one-year classes in a population of altogether 265,000 individuals in Sweden. The incidence of mental subnormality of these degrees was 7.1 per 1,000 boys and 5.8 per 1,000 girls in the ages 2–11 years. The distribution of different clinical types in this material was studied and the educability in the different clinical groups is discussed. The occurrence of complications concerning pregnancy, delivery and birth weight, as well as of signs of cerebral injury during the first week of life, was investigated in certain groups of the material. Half of the cases in the sporadic idiopathic oligophrenic group had early potential injury or signs of cerebral injury of the type described above. In a control material of unselected newborns, the corresponding figure was only 20 per cent. A comparison with a special, unselected series of children with cerebral palsy seemed to show that abnormal conditions concerning pregnancy, child birth and birth weight can be traced in sporadic idiopathic imbecility and idiocy almost as often as in cerebral palsy.

Etude de groupe du retard intellectuel chez l'enfant.

Investigation statistique de l'imbecillité et de l'idiotie dans un groupe d'enfants, comprenant 10 classes d'un an, et issus de 265000 parents suédois. La fréquence de

tels retards intellectuels entre 2 et 11 ans, peut être fixée à 7,1 pour mille chez les garcons, et 5,8 pour mille chez les filles. La répartition des divers types cliniques, ainsi que les possibilités éducatives de chaque groupe ont été étudiées. L'existence de facteurs étiologiques a été recherchée, notamment au cours de la grossesse ou de l'accouchement, le poids de naissance, et les signes de traumatisme cérébral observés dans la première semaine. Dans 50 % des cas d'oligophrénie essentielle, on retrouvait des signes de maladie cérébrale précoces. Ce pourcentage dans un groupe de nouveaux-nés témoins n'était que de 20 %. La comparaison avec un groupe d'enfants atteints de «paralysies cérébrales» semble montrer que de sfacteurs anormales en connection avec la grossesse et l'accouchement pathologique ou la prématurité peuvent être trouvés presque aussi frequents dans l'imbécillité et l'idiotie sporadique que dans la paralysie cérébrale.

Eine Übersichtsstudie über die geistige Unterentwicklung bei Kindern.

Beschrieben wird eine statistische Untersuchung über das Vorkommen von Imbezilität und Idiotie unter einer Gruppe von Kindern, welche 10 Ein-Jahr Klassen einer Bevölkerung von insgesamt 265000 Menschen in Schweden umfasst. Die Häufigkeit geistiger Unterentwicklung dieser Schweregrade betrug 7,1 auf 1000 Jungen und 5,8 auf 1000 Mädchen in den Altersstufen zwischen 2. bis 11. Lebensjahr. Die Verteilung der verschiedenen klinischen Gruppen in dieser Serie wurde studiert und die Erziehungsmöglichkeiten der verschiedenen klinischen Gruppen diskutiert. Bei gewissen Gruppen dieser Untersuchungsreihe wurde das Vorliegen von Komplikationen in der Schwangerschaft, bei der Entbindung, Geburtsgewicht und Zeichen einer zerebralen Schädigung während der ersten Lebenswochen untersucht. Die Hälfte der Fälle in einer Gruppe sporadischer idiopathischer Oligophrenie zeigte Hinweise auf Frühschädigungen oder Zeichen einer Gehirnschädigung von oben beschriebener Art. Bei einer Kontrollserie unausgelesener Neugeborener betrugen die entsprechenden Daten nur 20 %. Ein Vergleich mit einer speziell wahllosen Serie von Kindern mit zerebraler Kinderlähmung scheint zu zeigen, dass abnorme Schwangerschaft, Geburt und Geburtsgewicht betreffende Bedingungen bei der sporadischen idiopathischen Imbezilität und Idiotie genau so oft nachgewiesen werden wie bei der zerebralen Kinderlähmung.

Estudio extrahospitalario de la mentalidad subnormal en niños.

Se describe una investigación (censo) sobre la prevalencia de imbecilidad e idiocía comprendiendo 10 clases de 1 año correspondientes a una población de 265000 almas (Suecia). La incidencia de estos grados de subnormalidad fué de 7,1 para 1000 niños y 5,8 para 1000 niñas de 2 a 11 años. Se estudian los diferentes tipos clínicos, discutiendose la educabilidad de ellos. En ciertos grupos de estas series se estudió la incidencia de complicaciones durante la gestación y parto, peso al nacer y signos de daño cerebral durante la primera semana de vida. La mitad de los casos del grupo oligofrenia idiopática esporódica tuvieron probabilidades de daño temprano o signos de lesión cerebral. En un grupo control de recién nacidos no seleccionados, las cifras correspondientes fueros solo 20 %. Una comparación con series especiales no seleccionadas de niños con parálisis cerebral, parece mostrar que condiciones anormales referentes a embarazo, parto y peso al nacer, pueden actuar en idiocía e imbecilidad idiopáticas esporádicas casi tan amenudo como en la parálisis cerebral.

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Children's Hospital
Linköping, Sweden

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From the Department of Medical Biochemistry, University of Gothenburg, and the Pediatric Clinic, University of Uppsala

Protein Hydrolysis in the Stomachs of Premature and Full-term Infants

by RAGNAR BERFENSTAM, RUDOLF JAGENBURG and OLOF MELLANDER

It is generally assumed that the nutritional value of a protein is proportional to its digestibility and that proteins cannot be utilized, if they are not almost completely hydrolysed in the intestinal tract. This view is mainly based on experiments performed 30–40 years ago on animals or adults (for references see *Protein Metabolism* by R. B. FISHER, Chapter 1). Quantitative methods for amino acid assay were not available at that time and it seems apparent that the view that most of the protein is absorbed as amino acids is not supported by sufficient experimental evidence. Nevertheless, it is considered as more or less axiomatic that babies and especially premature babies are dependent upon the complete enzymatic breakdown of the food protein in the intestinal tract. When low enzymatic activity has been found, as for example in prematures, this has been considered as a sign of functional immaturity, and the therapeutic use of predigested protein has been introduced.

When studying the enzymatic hydrolysis of casein from human milk, one of us (MELLANDER 1947) found that this casein was much more resistant to the enzymes used than was cow's casein. This difference was found also when gastric juice from infants was used instead of enzyme preparations of animal origin. Thus, one of the proteins of the physiologic food, human milk, was found to be less "digestible" than the corresponding milk protein from another species (cow). These experiments were performed at optimal conditions of pH, enzyme concentration, and so on. From the hydrolysates, enzyme-resistant phosphorylated peptides were isolated and a difference in the quantities of such peptides formed was believed to be the reason for the difference in digestibility. Phosphorylated peptides were later (MELLANDER 1950, MELLANDER *et al.* 1950, ÅGREN *et al.* 1954 & 1954) studied concerning their metabolic importance, and the preliminary experiments so far published seem to indicate that they may be the carriers of fundamental functional properties.

It appeared of interest to the authors to investigate also the intact protein mixture in human and cow's milk concerning its digestibility under the most physiological conditions possible. In this paper, some experiments concerning the gastric digestion in both full-term and premature babies will be reported. Further experiments of a similar type concerning the intestinal digestion are in progress.

Method

Different test solutions were introduced through a tube into the stomach of premature and full-term infants. In all cases, the test solutions were fat-free breast milk or skimmed cow's milk—diluted with an equal part of water. All milk was pasteurized.

Samples of the gastric content were taken up at fixed intervals, this procedure proceeding as long as there was any yield, i.e. usually for about one hour. It may be remarked that in general it was more difficult to obtain a sufficient amount of gastric content when the test solution was cow's milk than in the case of breast milk. The protein precipitate observed especially in the cow's milk samples was always finely dispersed and passed through the tube without difficulties.

The samples were immediately neutralized with a few drops of 0.1 *N* NaOH to a pH of *c.* 8, and then frozen to $-15°C$ and kept in that state until analysed, as a rule 2–8 weeks later.

After thawing, the samples were added to twice the volume of *M*/15 phosphate buffer, pH 8.0. In order to remove any possible mucus (occurring in about half of the cases), the samples were filtered through a very thin and sparse layer of glass-wool, which was thereafter washed with buffer in order to remove protein fixed to the mucus. As has been shown by analysis, only negligible amounts of nitrogen were lost by this procedure.

After this operation, the samples of human milk were completely homogeneous, but the cow's milk samples showed varying degrees of casein precipitation.

The degree of digestion in the samples obtained was determined as percentage amino nitrogen of total nitrogen. The amino nitrogen was determined by the van Slyke-Neille method (PETERS & VAN SLYKE) and total nitrogen by the method of Kjeldahl (micro method).

In all cases where it was possible, i.e. in 82 % double determinations were performed both for amino nitrogen and for total nitrogen, with a standard deviation for duplicates of 4.2 and 2.7 per cent respectively.

Results

Altogether 28 digestion experiments were performed on 18 children of varying maturity. The series includes two pairs of twins. Apart from the prematurity no signs of disease were observed. Ten of the children were tested both with cow's milk and with human milk, eight children only with human milk. Table 1 gives the results from all experiments performed except one (one of twins), which was discarded because of regurgitation of

TABLE 1

In vivo digestion of milk proteins in the stomach of premature and full-term infants.

C = Cow's milk. H = Human milk.

Experiment No.	Age in days	Weight in g		% amino nitrogen of total nitrogen after minutes			
		at birth	on day of test	0	10	30	60
1 H	21	1810	1920	6.1		6.9	5.6
1 C*	25		2050	4.4		8.1	17.2
2 H	21	1690	1840	6.1		6.5	6.5
2 C*	25		1970	4.4		5.1	13.7
3 H	13	2030	2050	4.9		4.7	5.1
3 C	15		2040	4.9	5.9	5.9	9.0
4 H	30	2010	2430	6.6	7.4	7.5	7.4
4 C	24		2230	4.7	4.7	4.9	7.6
5 H	43	3180	3770	6.4	7.3	8.6	9.7
5 C	44			4.8	7.3	7.5	10.0
6 H	13	3550	3250	6.4	6.8	7.9	7.9
6 C	14		3250	4.8	7.2	9.3	10.3
7 H	24	2000	2170	6.1	6.0	5.5	7.5
7 C	23			4.7	5.2	7.0	10.0
8 H	36	1800	2500	6.1	—	6.2	7.1
8 C	35			4.7	5.6	6.4	10.4
9 H	18	1880	2130	7.1	7.6	7.8	8.6
9 C	19			5.0	7.1	11.1	10.4
10 H	25	2060	2200	7 1	8.1	8.1	8.2
10 C	26		2200	5.0	7.5	7.3	—
11 H	8	1680	1490	6.9		5.8	6.3
12 H	42	1820	1760	6.9		7.1	7.9
13 H	15	1880	1850	7.6		7.7	14.3
14 H	33	2240	2220	6.4	7.3	8.9	11.4
15 H	32	3200	3120	9.1	10.0	8.9	9.0
16 H	13	4540	4100	9.1	8.7	9.9	9.7
17 H*	6	2220	1990	5.2		5.9	6.0
Mean value of exp.							
1–17 H	23	2330	2400	6.6		7.3	8.1
1–19 C	25	2200	2430	4.8		7.3	11.6

* Twin.

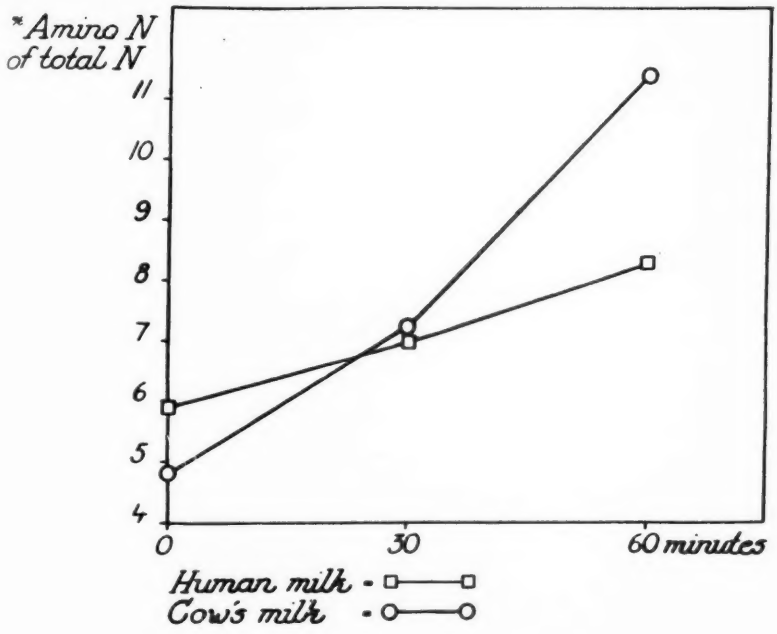

Fig. 1. *In vivo* digestion of cow's and human milk. Mean value of exp. 1–10.

the intestinal content into the stomach, indicated by a yellow discolouration. There was no visible admixture of bile in any other experiment. Fig. 1 gives the mean value of the group of ten children tested with both types of milk.

On an examination of the 17 experiments which have been made with human milk as substrate, great variations are to be seen in the relative content of amino nitrogen in the original samples. The amino nitrogen varies from 4.9 to 9.1 % of total nitrogen with a mean value of 6.1 %. The mean value for cow's milk is 4.8 %, with a variation from 4.4 to 5.0 %. This difference might be due to different amounts of free amino acids and lower peptides in the milks.

As a rule, there is no digestion at all, or a very slight one, in the experiment with human milk. This is the case also in the oldest and most mature babies. The experiments with cow's milk show a very good digestion even in the most premature infants, and no correlation seems to exist between birth weight or actual weight and degree of hydrolysis (Fig. 2).

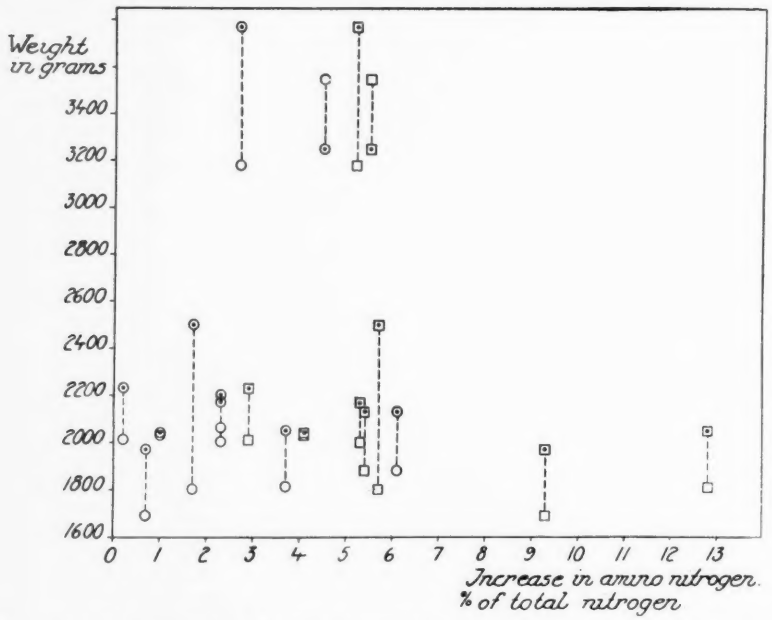

Fig. 2. *In vivo* digestion of cow's milk in correlation to weight at birth and on day of test.
○ After 30 minutes. Correlated to weight at birth.
○ ,, 30 ,, ,, ,, ,, on day of test.
□ ,, 60 ,, ,, ,, ,, at birth.
⊡ ,, 60 ,, ,, ,, ,, on day of test.

Discussion

The most striking result is the great difference which seems to exist in the digestibility of cow's and human milk. In all experiments, there is a significantly more complete digestion of the cow's milk. When in one and the same child experiments were performed with both cow's milk and human milk, on the average about 5 times more amino nitrogen was liberated by the digestion of cow's milk than by the digestion of human milk.

This result is in agreement with earlier investigations by among others ROSENBAUM and SPIEGEL, who incubated milk at different pH with stomach juice from children and determined the increase in soluble nitrogen. They found such an increase even at a pH value not favourable for pepsin activity, when the substrate was cow's milk, but not when it was human milk. BUDDE, too, has in both *in vitro* and *in vivo* experiments studied the liberation of amino groups by proteolysis of cow's and human milk. She found that almost twice the amount of amino groups were liberated when

the substrate was cow's milk. The reason for this, she thought, was the great amount of albumin in relation to casein in human milk. As one of us has shown (MELLANDER 1947), there exists, however, the same difference in the digestion of pure casein prepared from cow's milk and human milk, respectively.

The degree of immaturity, therefore, seems to be of minor importance for the gastric hydrolysis of proteins. The type of substrate on the other hand is of fundamental importance in that the proteins of human milk, which must be considered as the physiologic food proteins for the human baby, are subject to a very slight hydrolysis in the stomach as compared with the proteins of cow's milk.

Summary

The proteins of human milk are subject to a very slight hydrolysis in the stomach of babies, both premature and full-term. Cow's milk proteins are hydrolysed to a much higher degree, and this is independent of the maturity of the infant.

Hydrolyse des protéines dans l'estomac des prématurés et des nouveaux-nés a terme.

Les protéines du lait humain ne sont sujettes qu'à une hydrolyse très discrète dans l'estomac des prématurés, et des nouveaux-nés. Les protéines du lait de vache sont nettement mieux hydrolysée, et ceci est indépendant du degré de maturité de l'organisme de l'enfant.

Eiweisshydrolyse im Magen frühgeborener und ausgetragener Säuglinge.

Die Eiweissstoffe der menschlichen Milch unterliegen im Magen frühgeborener und ausgetragener Säuglinge einer sehr leichten Hydrolyse. Kuhmilcheiweiss wird in viel grösserem Ausmass hydrolysiert; auch diese Hydrolyse ist unabhängig von der Reife des Säuglings.

Hidrólisis de proteínas en el estómago del prematuro y del niño de término.

Las proteínas de la leche humana sufren una pequeña hidròlisis tanto en el estomago del prematuro como del niño de término. Las proteínas de la leche de vaca son hidrolizadas en grado mas alto, siendo esta independiente del grado de madurez del niño.

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Department of Medical Biochemistry
University of Gothenburg,
Gothenburg

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From the Children's Hospital, University of Oslo, Norway
(Head: Professor LEIF SALOMONSEN)

The Reticulocyte Level, and the Erythrocyte Production Judged from Reticulocyte Studies, in Newborn Infants during the First Week of Life

by MARTIN SEIP

ISRAEL & PAPPENHEIM (1896) demonstrated that fetuses from various animal species had high reticulocyte levels. Staining with methylene blue, BIDONE & GARDINI (1898) discovered that newborn infants had a reticulocytosis, which was most marked in prematures. As early as 1871 NEUMANN found nucleated red cells in the peripheral blood of normal newborns. The reticulocytosis during the first days of life was also found by SABRAZÈS & LEURET (1908), who were able to show that the reticulocyte values decreased rapidly in a few days to "normal" or "subnormal" levels.

A classification according to HEILMEYER (Fig. 1) of the reticulocytes in the peripheral blood of newborn infants (RASI & BOLLETTI 1938, WEGELIUS 1948) shows that the least mature reticulocytes (his stages I and II) are relatively numerous. This could also be expected, since there is even a certain number of nucleated red cells in the circulation (stage 0 according to Heilmeyer's classification).

In fetal life the blood contains a still greater number of nucleated red cells and reticulocytes than after birth, especially during the earliest months of gestation. According to WINDLE (1941) there are about 90 % reticulocytes in the blood of the human fetus at three months of age, 15–30 % at six months of age, and 4–6 % at birth.

Most authors have found considerable variations in the reticulocyte count in different infants, and the values found by different authors are extremely variable (Table 1). Some authors have found that the decrease in reticulocyte level starts almost immediately after birth (KRUMBHAAR, SEYFARTH & JÜRGENS, FAXÉN), others have found a slight or moderate transitory rise for some hours (up to 48 hours) after birth (CATHALA & DAUNAY, BRAHMACHARI, RASI & BOLLETTI, WAUGH *& al.*, WINDLE, WEGELIUS).

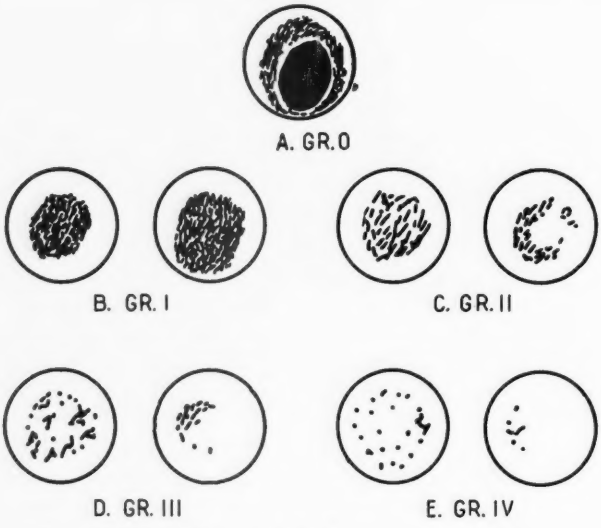

Fig. 1. Diagram illustrating the five groups of reticulocytes (Heilmeyer and Trachtenberg).

TABLE 1

The reticulocyte levels in the peripheral blood in normal infants during the first day of life. (According to the literature.)

Authors	Year published	Average percentage of reticulocytes	Range of variation
Krumbhaar	1922	4.7	
Seyfarth & Jürgens	1927	6.2	5–10
Forkner	1929	1.91	
Kato	1932	1.63	
Merritt & Davidson	1933	3.4	1.8–5.5
Brahmachari	1934		1.2–4.8
Josephs	1936		4–6
Faxén	1937	2.5	
Wollstein	1938		1.2–2.6
Waugh, Merchant & Maughan	1939	2.7	0.2–5.9
Shapiro & Bassen	1941	2.3	1.0–4.7
Windle	1941		4–6
Wegelius	1948	2.8	

The remarkably great discrepancies in the reticulocyte percentage at birth found by the authors referred to in Table 1 can only be explained by the fact that methods of highly different degree of sensitivity have

been used. Those authors who have the lowest average values have used the least sensitive and therefore least suitable methods.

In addition to being sensitive a good procedure for making reticulocyte counts also should have a reasonable, *not too great counting error*, and the approximate magnitude of this error *should be known*. It appears from Table 1 that several authors have found an astonishingly large range of variation for the normal reticulocyte level at birth, e.g. from 0.2 to 5 ‰, or from 1 to 4.7 ‰. These large variations are certainly not real, but can only be explained by the counting error being too great. This may have the following reasons: (1) a relatively small number of erythrocytes has been counted in each preparation (500 to 1,000); (2) the distribution of the reticulocytes in the preparations has been disproportionally uneven (MARCUSSEN); or (3) the sensitivity of the method has varied from time to time, depending on how carefully the preparations have been prepared and examined.

Methods

Reticulocyte counts.—A previously described method (SEIP) has been used in slightly modified form. A solution of brilliant cresyl blue 1 % and sodium citrate 0.4 % in normal saline has been used as a stain.

One to two drops of heel blood is mixed well with an equal amount of staining fluid in a hollow-ground, silicone-coated slide. The mixing is done by means of a small glass rod, which is also silicone-coated. The slide is placed in a moist chamber for 20 minutes. The stained blood is thereafter stirred very well with the glass rod, so that an even suspension is obtained. Thin smears are then made on thoroughly cleaned slides. The procedure, as a rule, gives good preparations. The use of 3–4 drops of venous blood along with 3–4 drops of dye is still better.

As a rule, 2,500 erythrocytes are counted in two separate areas in each preparation, that is a total of 5,000 cells. The reticulocytes are classified according to Heilmeyer's classification. Thereby an estimation of the degree of maturity of the reticulocytes is obtained. Furthermore, when doing such a classification one is forced to examine the smears very carefully, which is an added safeguard toward accuracy. In these investigations the author has performed all reticulocyte counts personally.

Technical errors.—Using the procedure described the author found in blood of normal adults that the standard deviation due to technical errors was 1.07 ‰ for total number of reticulocytes, when the counts were performed on the same day, and 1.52 ‰ when they were performed on different days. The reticulocyte level is higher during the first few days of life than in adults, and the standard deviation for the counts, expressed in per mille, is slightly higher also in this period.

Determination of the erythrocyte production in the newborn.—The author has used a method described in detail elsewhere. It is based on the following theoretical prerequisites: (1) that all red cells leave the blood-producing organs as reticulocytes, passing the last part of the reticulocyte stage *in the circulating blood*. In this connection the nucleated red cells found in the blood of healthy newborn infants are also regarded as reticulocytes since they contain reticulum. (2) that the maturation of the

reticulocytes to fully mature, non-reticulated erythrocytes procedes with approximately the same velocity in vitro at body temperature as in vivo.

That these assumptions usually hold true has been shown in another publication (1953).

The blood is withdrawn under sterile precautions and incubated at 37° C in small, sterile, silicone-coated test tubes. Reticulocyte counts are performed after incubation for various lengths of time, e.g. at four hour intervals. From the reticulocyte maturation curves thus determined, the production of red cells can be calculated. The decrease in percentage of reticulocytes per time unit during the first part of the incubation is a direct estimate of the erythrocyte production.

Results of the Investigations

Thirteen healthy, full term newborns, 7 males and 6 females, have been studied during the first day of life. In 6 cases cord blood was taken at birth, in the others heel blood 2–13 hours after birth.

The average reticulocyte content of the blood was 51.9 per mille, with variations from 41.6 to 63.0. In normal adults the author found an average of 15.7 ‰ (range of variation: 9.6–23.8) with the same method. In most cases cord blood contained about 300,000 reticulocytes per c.mm, but the individual variations were considerable. The average reticulocyte formula (HEILMEYER) was as follows, with corresponding figures for normal adults listed in parentheses: Gr. I: 4.6 ‰ (0.02), Gr. II: 18.3 ‰ (1.1), Gr. III: 16.0 ‰ (5.0), Gr. IV: 13.1 ‰ (9.5). The reticulocyte percentage at birth is related roughly to the duration of gestation, other factors being normal. It is lower in full term than in premature infants, and lower still in postmature infants (Fig. 2).

In a previous study the author was able to demonstrate that most of the erythrocytes normally are released from the bone marrow as reticulocytes in stage III in older children and in adults, some in stage II, and an occasional cell in stage I. When for one reason or other (breathing in an atmosphere with low oxygen tension, anemia, etc.) the oxygen supply to the body decreases, then the red cells will enter the circulation in an earlier stage of their development. This is also true in fetal life and in newborns. In healthy infants at birth most of the red cells leave the blood-forming organs in stage II, some in stage I, and a few as nucleated red cells.

When the cord is clamped, a certain portion of the fetal blood will remain in the placenta and umbilical vessels, and more by early than by delayed clamping of the cord. The young red blood corpuscles entering the circulation shortly after birth will be distributed in a smaller amount of blood than the red cells produced just before birth. A transitory rise in the reticulocyte content of the blood therefore does not necessarily mean

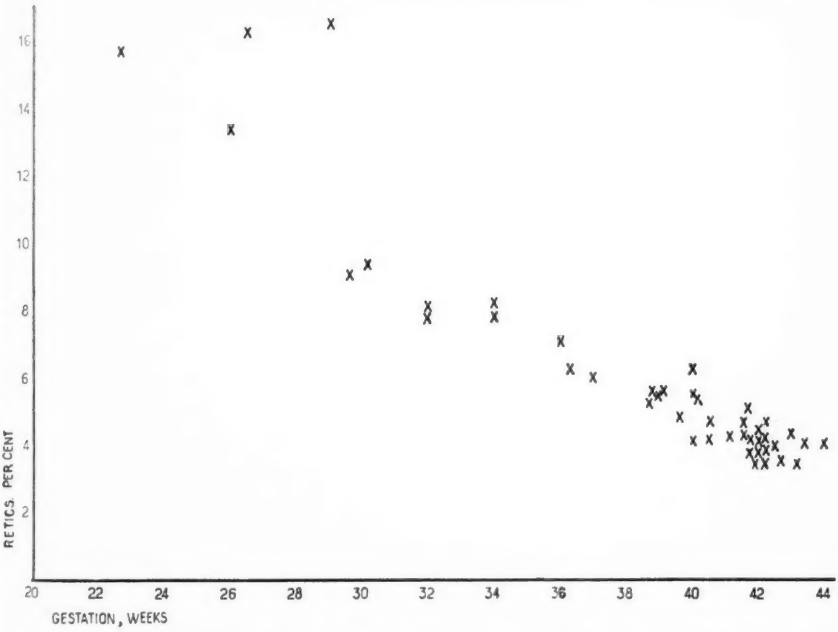

Fig. 2. Reticulocyte counts at birth in premature, fullterm, and postmature infants without compl. diseases.

that the erythrocyte formation has been increased after birth. A very early clamping of the cord leads to a higher reticulocyte level than a delayed clamping of the cord, provided the production of red cells is equal in either case. WINDLE actually was able to demonstrate such a difference between cases with early and delayed clamping of the cord. However, he thought the difference was due to a more intensive erythropoiesis in the former.

To determine the normal day-to-day fluctuations in the reticucolyte content of the blood and in the erythrocyte production during the first week of life, reticulocyte counts were performed at 24-hour intervals in 8 healthy newborns (Fig. 3). Even though the original reticulocyte percentage varies from one baby to another, the trend of the curves is astonishingly similar in all cases. The reticulocyte content of the blood is high and approximately constant for about three days after birth. The counts performed on the fourth day show a small, but statistically significant decrease. *From the first half of the fourth to the first half of the sixth day of life, all infants had a rapid, pronounced drop in the reticulocyte level.* From the sixth

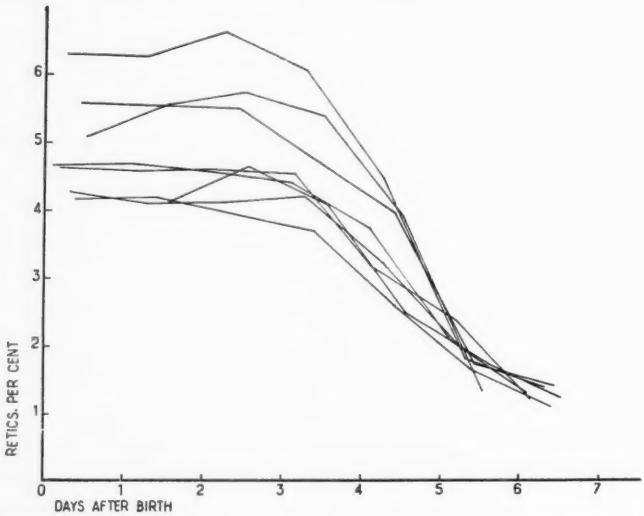

Fig. 3. The reticulocyte levels in 8 normal newborn infants during the first week of life.

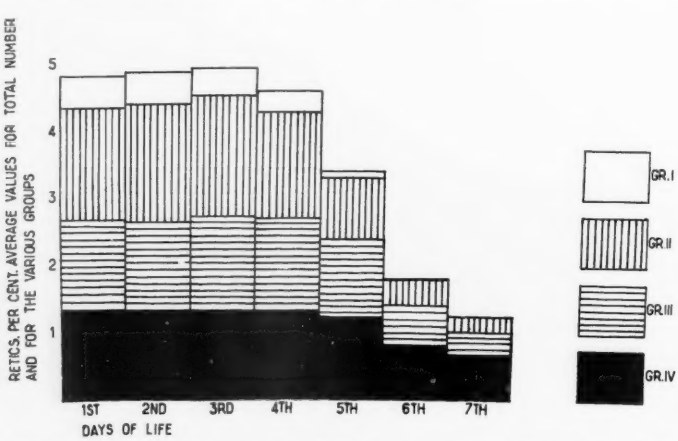

Fig. 4. Average reticulocyte formulas in eight newborn infants during first seven days of life.

to the seventh day there is a further, though slower decrease to values corresponding roughly to normal adult values.

In three cases the reticulocyte content of the blood showed a mild, transitory rise from the first to the third day. Although the rise was near the upper limits of the counting error, it was probably real, and can be

explained as outlined above by the amount of fetal blood remaining in the placenta and cord vessels after the clamping of the cord.

The average values for the first seven days of life appear in Fig. 4. The decrease occurs first and to the greatest extent among the most immature forms, indicating that the red cells are leaving the blood-forming organs at a later stage of their development than they did at birth. On the seventh day the reticulocyte formula is approximately as in normal adults, with the following average values (range of variation in parentheses): Gr. I: 0.1 ‰ (0–0.4), Gr. II: 2.3 ‰ (1.4–3.2), Gr. III: 3.6 ‰ (2.6–4.0), Gr. IV: 6.8 ‰ (6.4–7.6). Total: 12.7 ‰ (10.8–14.0).

The author could not confirm the finding reported by WEGELIUS of a marked reticulocyte peak two hours after birth.

Discussion

It has already been mentioned how the production of red cells can be determined with a reasonable degree of accuracy by studying the maturation of the reticulocytes in vitro at 37°C, provided that the reticulocyte counts are performed with extreme exactitude. Incubation experiments with cord blood from 6 healthy newborns have been performed. The reticulocyte maturation curves are shown in Fig. 5. They are approximately rectilinear in the part of their course which has been determined. Theoretically, the different points in each experiment should be on a straight line, the course of which can best be calculated by the method of least squares. When doing so, it is found that between 24 and 30 ‰ of the red cells in these experiments have matured from reticulocytes to fully mature, nonreticulated erythrocytes within 24 hours of incubation, in other words, 24–30 mature erythrocytes per 1,000 red cells present have been formed in the course of 24 hours. The results from the 6 experiments showed 24, 25, 25, 26, 27, and 30 ‰. In the blood of normal adults of both sexes the author found in similar experiments that the formation of mature erythrocytes was on an average 9 ‰ of the total red cell mass per day. This is in conformity with the values for the daily erythrocyte production in healthy adults, which can be calculated from differential agglutination experiments and other red cell survival studies.

When comparing the formation of erythrocytes and hemoglobin in the newborn infant and in adults, the question arises, which basis is the most appropriate for the comparison. We can express the erythrocyte production per day in percent of the organism's total red cell mass. We will then, for the experiments just discussed, find 0.8–1.0% in normal adults, compared to 2.4–3.0% in normal newborns at birth, i.e. an erythrocyte production in the latter that is about three times as intensive.

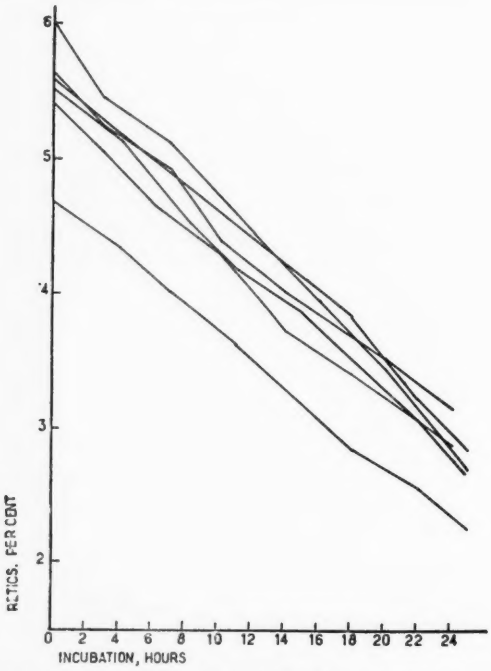

Fig. 5. Reticulocyte maturation curves in cord blood from six healthy newborn infants.

The erythrocyte production can also be expressed by the number of erythrocytes produced per c.mm blood per day. In this case, the figures for infants at birth (about 150,000) will also be about thrice the corresponding adult figures, because the red cell content is approximately the same in cord blood as in blood from adults. The difference in *formation of hemoglobin* per c.mm blood per day, however, will be somewhat greater, because the average red cell is richer in hemoglobin at birth.

Finally, if we want to compare the hemoglobin formation *in relation to the body weight*, the difference will be still more pronounced. The blood volume of an infant at birth is greater than in an adult in relation to the body weight, at least if we (before the cord is clamped) include the fetal blood present in the placenta. The formation of hemoglobin per kg body weight is at least four, perhaps even five times as rapid in the infant at birth as in normal adults. The average newborn baby is supposed to contain a total amount of about 60 g hemoglobin. A formation of 2.5 % of the total hemoglobin per day therefore will amount to 1.5 g, or 0.43 g/kg body weight/day in an infant weighing 3.5 kg. The average hemoglobin

formation is said to be 0.09 g/kg body weight/day in healthy adult males (CROSBY & AKEROYD), possibly slightly higher.

The calculations just presented are based on several factors, which cannot be determined with a high degree of accuracy, and the resulting figures must be considered as relatively rough estimates. We may conclude that the formation of erythrocytes and hemoglobin at birth in comparison with normal adults is three to five times as rapid, varying with the basis on which the comparison is made. It is, therefore, not astonishing that the newborn infant uses its bone marrow tissue throughout the body, and even the liver and spleen, for this intensive erythropoiesis. In certain conditions with long lasting, pronounced stimulation of the bone marrow, e.g. from severe congenital spherocytosis, adults can also increase their blood production greatly. In one case of this disease the author found an erythrocyte formation about five times and a hemoglobin formation about six times the normal average. CROSBY & AKEROYD found in similar cases that the daily hemoglobin formation probably could be up to seven times the normal average, this, however, representing the maximum reserve capacity of the bone marrow in adults.

We have no reasons to believe that the rapidity of the reticulocyte maturation process is substantially changed in the first few days of life. Therefore, the changes in the reticulocyte content of the blood will represent a reliable picture of the changes in erythrocyte production. The intensive erythropoiesis continues nearly unaltered for about three days after birth. Investigations on the hematopoietic activity in the liver of newborn infants (LANGLEY) lead to the same conclusion. The number of hematopoietic foci in the liver remains approximately unchanged in the first three days of life. Thereafter, the hematopoiesis in the liver subsides rapidly.

However, the reticulocyte curves presented indicate that there is *a slight decrease* in the erythropoietic activity even in the first three days of life, because otherwise we should have expected a more pronounced postnatal rise in the reticulocyte content of the blood. Another finding also strongly indicates that a slight decrease in the erythropoietic activity is already taking place a few hours after birth: the falling number of nucleated red cells in the circulation. When the formation of red cells decreases in intensity, the first hematologic sign will usually be the disappearence from the circulation of the very youngest erythrocytes present at the height of erythropoietic activity. When the erythropoietic activity diminishes after birth, we must expect to find a decrease in number of nucleated red cells earlier than in reticulocytes belonging to the more mature groups. The content of nucleated red cells in the peripheral blood of healthy newborn

infants is known from quite a few publications (LIPPMAN, BÜNGELER & SCHWARTZ, SHAPIRO & BASSEN, FINDLAY, and others), especially from LIPPMAN's excellent report.

LIPPMAN was able to demonstrate the presence of nucleated erythrocytes in the peripheral blood in almost every healthy newborn infant examined at birth or shortly after, on an average about 500 per c.mm. However, as early as 6 hours after birth the nucleated red cells had decreased slightly in number, and at the age of 12 hours the infants had only half as many nucleated red cells in the circulation as at birth. Forty-eight hours after birth the average was 26 erythroblasts per c.mm, and a few days thereafter they would normally disappear completely from the circulation.

From the reticulocyte studies reported in this publication and from the studies on nucleated red cells reported by LIPPMAN and others, we can conclude, that the erythrocyte formation is very rapid at birth and *approximately* of the same intensity in the first three days of life, although a *slightly declining tendency* is apparent as early as 6 hours after birth. On the fourth day, the decrease is so evident that a significant fall in the reticulocyte level is found. From the first half of the fourth day of life, the erythrocyte production diminishes rapidly within 2—3 days to normal adult levels.

Why do these dramatic changes in reticulocyte level and formation of red cells and hemoglobin take place? Most authors have believed that they are caused by the improved oxygen supply after birth. Under normal conditions the erythropoietic activity is, within certain limits, governed by the oxygen tension in the organism. There are also several authors (KRAFKA, WASHBURN, WINDLE) who have explained the neonatal changes in reticulocyte level and erythrocyte formation by growth factors. But the changes are so pronounced, and are taking place so rapidly, that the probability that they can be produced exclusively by variations in intensity of growth is extremely small, even though such variations may play a limited, quantitatively unimportant role.

The importance of changes in oxygen tension in this connection is evident from a series of reticulocyte counts in asphyxiated newborn infants. Newborn infants without complicating blood diseases, weighing 2,500 g or more at birth, have been studied. The underlying disorders were congenital malformations of the heart and trachea, or pulmonary disease, in one case also cerebral hemorrhage. It will be seen from Fig. 6 that the normal decrease in reticulocyte level is delayed in the asphyxiated babies. The delay corresponds roughly in time to the duration of the asphyxia. In an infant suffering from severe cyanotic heart disease we found 4 % reticulocytes in the circulation as long as seven weeks after birth.

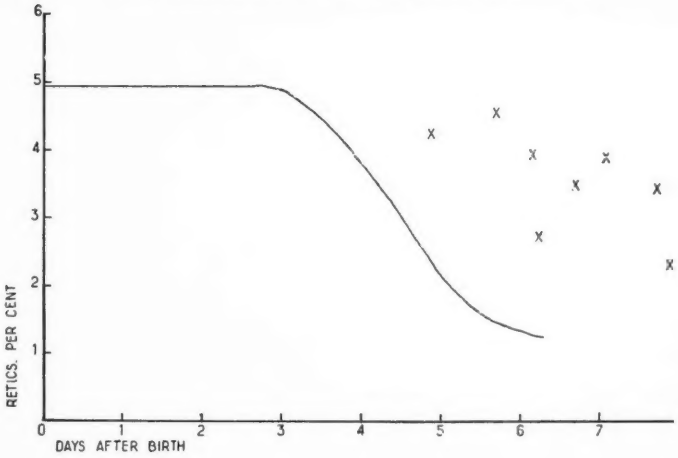

Fig. 6. Reticulocyte counts in newborns with prologed asphyxia (crosses). The "typical" trend of the reticulocyte curve in healthy newborn infants is illustrated by the solid line.

Another interesting problem also arises. Why do as much as three days elapse, until the reticulocytosis and the erythropoietic activity are substantially reduced, whereas the oxygen saturation reaches normal, high values within a few hours after birth in healthy newborn infants (SMITH & KAPLAN)? In the author's opinion the most satisfactory answer can be given on the basis of a theory for explanation of the normal regulation of the organism's erythropoietic activity, which is outlined in a previous publication (1953). According to this theory, the oxygen tension does not exert its effects on the liberation of reticulocytes into the circulation and on the erythrocyte formation directly and instantaneously in the blood forming organs. The decisive factor is the oxygen tension in a blood regulating center (probably located in the brain stem), and this center exerts its regulating influence to a large extent by provoking the formation in the body of humoral, reticulocytosis-producing and erythropoiesis-stimulating substances. The author was able to demonstrate the presence of a such substance (or such substances) in plasma from newborns with erythroblastosis, by injecting the plasma into healthy adults (1953). That it is present in normal cord plasma at birth as well will be shown in a later publication. It seems reasonable to assume that the presence of these substances in high concentrations in the body at birth (caused by the poorer oxygen supply in fetal life), will continue to stimulate the erythropoiesis for a few days after the oxygen tension has reached normal post-

natal values, because a certain time is required for these substances to be consumed by the organism; this at least may be part of the explanation for the rapid erythrocyte formation during the first 3–4 days of life.

Summary

The main purpose of this study has been to investigate the reticulocyte content and reticulocyte maturation time in the peripheral blood during the first week after birth, in order, thereby, to elucidate the formation of red cells and hemoglobin in this period of life. The considerable discrepancies found in the literature on this subject are to a large extent due to the fact that unsatisfactory methods have often been used.

The author's methods are described. The reticulocytes have been classified in various stages of maturity according to HEILMEYER's classification (Fig. 1). Much attention has been paid to the problem of reducing, as far as possible, the technical errors involved in the counts.

On the first day of life 51.9 reticulocytes per 1,000 red cells was found as an average in healthy, full-term newborn infants, with variations ranging from 41.6 to 63.0. In blood of normal adults examined by the same method, the average was 15.7 ‰ (9.6–23.8). The average reticulocyte formula for the first day of life was as follows, with the corresponding adult figures in parentheses: Gr. I: 4.6 ‰ (0.02), Gr. II: 18.3 ‰ (1.1), Gr. III: 16.0 ‰ (5.0), Gr. IV: 13.0 ‰ (9.5). The percentage of reticulocytes in the circulation is lower in full-term than in premature infants, and lower still in postmature babies (Fig. 2). The red cells leave the blood forming organs in an earlier stage in newborn infants than in adults.

The normal day-to-day changes in the reticulocyte content in the peripheral blood during the first week of life appear in Figs. 3 and 4. The reticulocyte level is high and remains approximately constant for three days after birth, whereafter a rapid drop occurs in the following 2–3 days, so that normal adult levels are finally reached. In some cases, especially if the cord is clamped early, a transitory rise in the reticulocyte level can be observed after birth. This is not caused by an increase in erythrocyte production, but is due to the fact, that the infant by the clamping of the cord is deprived of the blood present in the placental circuit, whereby the reticulocytes formed are distributed in a smaller amount of blood than immediately before birth.

The formation of erythrocytes and hemoglobin at birth is 3–5 times as rapid as in healthy adults, depending on the basis on which the comparison is made (Fig. 5). In terms of hemoglobin synthesized per kg body weight/day the relationship is probably almost 5:1. The erythrocyte production continues to be very rapid and not markedly changed for about 3 days after birth. Then it diminishes rapidly to normal adult levels within 2 or 3 days. A *slightly declining tendency* in erythrocyte formation, however, is found as early as 6 hours after birth.

By studying newborn infants with prolonged asphyxia from various causes it could be demonstrated convincingly, that the dramatic changes in reticulocyte level and rate of erythrocyte formation in the first week of life are related to the alterations in oxygen supply after birth (Fig. 6).

A discussion is also offered as to why a significant decrease in the reticulocyte level and erythrocyte formation does not take place until about 3 days after birth, whereas the oxygen saturation of the blood rises to normal, high levels in a ver

short time. One reason may be the presence of a humoral, reticulocytosis-producing and erythropoiesis-stimulating substance in relatively high concentrations in the organism at birth. This substance (or substances) supposedly requires a certain time to be consumed by the organism. The author has been able to demonstrate the presence of reticulocytosis-producing substances in plasma from newborn infants suffering from erythroblastosis, and in normal cord blood at birth.

Le taux des réticulocytes et la formation d'hématies estimées par l'éude des réticulocytes chez le nouveau-né au cours de la première semaine de la vie.

Le taux moyen des réticulocytes observé le premier jour chez des nouveaux-nés sains, à terme, était de 51,9 pour 1000 hématies, avec des variations entre 41,6 et 63,0. Chez l'adulte normal, la moyenne était de 15,7 pour 1000. Le pourcentage des réticulocytes circulants est plus faible chez le nouveau-né que chez le prématuré; il est encore plus bas chez le post-maturé. Les hématies quittent donc les organes érythropoïétiques plus tot chez le nouveau-né que chez l'adulte. La réticulocytose est élevée, et le demeure durant les 3 jours qui suivent la naissance: aprés quoi, s'amorce une chute brutale les 2 ou 3 jours suivants; on observe alors un taux analogue à celui de l'adulte. La formation d'hématies et d'hémoglobine à la naissance est 3 à 5 fois plus rapide, que chez l'adulte normal. Au bout de 3 jours, la formation d'hématies diminue rapidement, et atteint des valeurs égales à celles de l'adulte en 2 à 3 jours. Il n'a pu etre prouvé que ces modifications dans la réticulocytose et l'érythropoïèse étaient sous la dépendance de variations de l'oxygénation aprés la naissance.

Retikulocytenspiegel und Erythrocytenproduktion beim Neugeborenen in der ersten Lebenswoche beurteilt nach den Retikulocyten.

Beim ausgetragenen Neugeborenen wurden am 1. Lebenstag 51,9 Retikulocyten auf 1000 Erythrocyten als Durchschnittswert mit Variationen zwischen 41,6 und 63.0 gefunden. Bei normalen Erwachsenen betrug der Durchschnittswert 15.7 auf 1000. Der Prozentsatz zirkulierender Retikulocyten ist beim ausgetragenen Kind niedriger als bei frühgeborenen Säuglingen, noch niedriger jedoch bei übertragenen Kindern. Die roten Blutkörperchen verlassen die Blutbildungsorgane beim Neugeborenen früher als beim Erwachsenen. Der Retikulocytenspiegel ist hoch und bleibt etwa 3 Tage nach der Geburt konstant, wonach in den folgenden 2–3 Tagen eine rapide Abnahme bis zu den normalen Erwachsenenwerten einsetzt. Die Erythrocyten- und Hämoglobinbildung bei der Geburt geht 3–5mal rascher vor sich als beim gesunden Erwachsenen, abhängend von der Basis, auf welcher der Vergleich gezogen wurde. Nach dem 3. Lebenstag sinkt die Erythrocytenproduktion rapid innerhalb von 2–3 Tagen auf den normalen Spiegel bei Erwachsenen ab. Es konnte gezeigt werden, dass die dramatischen Änderungen des Retikulocytenspiegels und der Erythrocytenbildungsrate in der ersten Lebenswoche mit den Änderungen der Sauerstoffversorgung nach der Geburt in Beziehung stehen.

El nivel de reticulocitos y la producción de eritrocitos juzgados a través de la función reticulocítica en recién nacidos durante la primer semana de la vida.

Recién nacidos sanos y de término presentan en el primer dia de la vida, una cifra media de 51,9 reticulocitos por 1000 glóbulos rojos, con variaciones entre 41,6 y 63,0. En adultos normales, la cifra media es de 15,7 por 1000 g. r. El porcentaje de reticulo-

citos circulantes es mas bajo en recién nacidos a término que en prematuros, siendo aun mas bajo en los postmaduros. Los globulos rojos migran fuera de los órganos hematopoyéticos mas temprano en los recién nacidos que en los adultos. El nivel de reticulocitos es alto y permanece casi constante los tres primeros días de la vida, en los 2–3 dias subsiguientes ocurre una rapida caída hasta llegar a cifras que son normales en adultos. La formacion de eritrocitos y hemoglobina al nacer es 3 a 5 veces mas rápida que en los adultos sanos, variando según las bases tomadas como comparación. Después del tercer día de la vida, la producción de eritrocitos disminuye rápidamente hasta alcanzar niveles normales en la edad madura. No pudo ser demostrado que los bruscos cambios de nivel reticulocitario y formación de eritrocitos en la primer semana de la vida tengan alguna relación con la administración de oxígeno al nacer.

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Children's Hospital
University of Oslo
Oslo, Norway

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PROGRESS IN PEDIATRICS

Cutaneous Hemangiomas in Premature and Mature Infants

by KURT HOLMDAHL

From the Pediatric Clinic of the Children's Hospital, Gothenburg (Head: Prof. Y. Åkerrén)

Nomenclature

Terminology and classification of hemangiomas is confusing and complicated. ANDRÉN suggested a classification which is suitable for clinical practice:

1. Hemangioma capillare
2. Hemangioma cavernosum
   a. Hemangioma cavernosum superficiale
   b. Hemangioma cavernosum profundum
   c. Mixed types

To complete this classification a third group might be added containing more rare forms of hemangiomas, e.g. the racemous, arterial and pulsating angiomas, and naevi aranei, spider naevi.

The *capillary* hemangiomas, also called teleangiectasis, are composed of two forms, the naevi flammei and naevi vinosi. The naevi vinosi at times exhibit a tendency to grow and form cavernous angiomas. The capillary angiomas consist of densely packed capillaries with a highly differentiated endothelium. The clinical appearance is that of light red to violet formation, which is not elevated above the level of the surrounding skin. Their growth is proportionate to that of the skin. Naevi flammei usually regress.

The *cavernous* angioma is made up of communicating bloodfilled spaces. The endothelium may either be highly differentiated, or in some cases resemble a more embryonal structure. POTTER has described the different histological appearance of the superficial and the deep cavernous hemangiomas. She found that endothelial proliferation was characteristic of the superficial angiomas, and calls them "hypertrophic endothelial hemangiomas". In this type there are anastomosing capillaries and small blood vessels, which exhibit varying degrees of endothelial proliferation. She calls the deep type "cavernous hemangiomas". They are characterized by wide anastomosing cavities lined by endothelial cells and separated by varying amounts of connective tissue. Undifferentiated endothelial cells are also sometimes present, but often the only solid portions are the connective tissue trabeculae.

The clinical appearance is related to the difference in the histological pictures. The *superficial* hemangiomas are slightly elevated from the skin, and red to purple in colour. They have a rough surface and resemble "strawberry" naevi. Their growth is rather rapid during the first months but very seldom exceeds a diameter of 1–3 cm. The *deep* hemangiomas are found under the skin or mucous membrane, occasionally in internal organs. Their size is more variable and may involve large part of the body.

They may extend to superficial layers of the skin, in which case a transitorial form of superficial angiomas arises. Their colour is a deep blue or if deep to the skin they may appear only as a swelling. Such hemangiomas may enlarge slowly. If the blood vessels are large and superficial, necrosis of the skin may be followed by bleeding.

ANDRÉN, RAMBAR and others maintain that the superficial hemangiomas usually appear after birth, whereas the deep cavernous hemangiomas are present at birth. From the clinical as well as the histological point of view this emphasizes the difference between the two types. At times, however, it is very difficult to distinguish between the two. Since ANDRÉN's nomenclature is appropriate, it will be used in this report.

History

It is difficult to study the literature because of the varying nomenclature. This is no doubt one of the reasons for the many contradictory statements concerning these tumors.

According to the literature, hemangiomas most frequently involve the skin of the head and neck. These statistics have, as a rule, been compiled by investigators who have had the children sent to them for treatment and their statistics imply an increased frequency of hemangiomas in these areas. In these investigations often capillary angiomas which no doubt are more common in the face and neck (BELLOT) were included. Even those who have made a distinction between cavernous and capillary angiomas report that the cavernous angiomas are found more often in the skin of the head and neck. BELLOT found 77.4 per cent in this area. In a synopsis of cutaneous cavernous angiomas, 70 per cent of which were superficial, STRANDQVIST (1939) found 47 per cent localized to the head. He also found many angiomas in the midline or in the region of embryonal fissures. A selection of those causing cosmetic disturbance is apparent in this material. RAMBAR did not perform such a selection in his investigation. In 60 hemangiomas (almost all of the superficial cavernous type) he found 25 per cent on the head and neck, 31.6 per cent on the extremities, and 43.2 per cent on the trunk and the genital organs.

Most authors agree that hemangiomas are not always present at birth. Some maintain, however, that, as a rule they can be found at birth (FITZ-WILLIAMS *et al.*). BLAND-SUTTON *et al.* state that they appear later in most instances. In many reports it is difficult to determine the type of angiomas involved. This is important because the capillary and deep cavernous angiomata almost always are present at birth (DEPAUL). Opinions differ in regard to the superficial angiomas. Some state that most are present at birth. In many reports this information is based on the mothers' statements. RAMBAR seems to have investigated his cases with care. Of 40 children 7 had angiomas at birth. Of these 4 were deep cavernous angiomas and one a naevus vinosus. The remaining angiomas appeared between the first week and second month. ANDRÉN was of the same opinion as RAMBAR, i.e., that most hemangiomas of this type appear after birth.

The frequency of hemangiomas is stated differently. According to DEPAUL, one third of the newborn have capillary angiomas. The deep cavernous type is reported as more rare than the superficial (RAMBAR, ANDRÉN). Among 344 prematures RAMBAR found 40 (11.6 %) with hemangiomas, four of these were deep cavernous angiomas and

one a naevus vinosus. Naevi flammei were not registered. There is a widely accepted belief that the superficial cavernous angiomas are more frequent in prematures. Hess *et al.* found this type of hemangiomas in the skin in 8 of 250 prematures (3.2 %) and in two of 156 mature infants (1.3 %). Hemangiomas are regarded as more frequent in prematures with lower birth weights. Hess did not find an angioma in any premature with a birth weight more than 2,000 g.

The future development of the hemangiomas has its practical importance. The indications for treatment in part depend on this. Naevus flammeus has a tendency to disappear spontaneously. Naevus vinosus grows with the skin and does not respond to X-ray treatment. The deep cavernous angiomas as a rule grow in proportion to the surrounding tissues. Sometimes they exhibit a more rapid growth. Spontaneous regression seldom occurs. The superficial cavernous hemangiomas are different. Many authors have shown that they disappear spontaneously (Lister, Hopkins). On the other hand some maintain that they may not disappear, but continue to grow (Andrews). Of Rambar's 40 cases, 24 received X-ray treatment. He noticed a spontaneous regression in children over 6 months' age with "moderately large lesions". Strandqvist (1944) is of the opinion that there is a tendency to spontaneous regression. At best they slowly diminish in size and eventually disappear as the child grows older. He thinks they should be treated as early as possible, the optimal age being 2 months. Andrews *et al.* share this opinion.

Reese (1949, 1951) found superficial hemangiomas in 15 per cent of the prematures with retrolental fibroplasia. When comparing the results of his study with those of Hess and co-workers he concluded that hemangiomas were more frequent in prematures with retrolental fibroplasia. Hepner *et al.* could not confirm this.

A special position is, as appears from the above, held by the superficial cavernous hemangiomas. They are not present at birth and they appear to show a tendency both of growth and regression. They are supposed to be more frequent in prematures and still more so in prematures with retrolental fibroplasia.

This investigation is intended to determine in prematures and mature infants the type of the superficial cavernous hemangiomas, their localization, the time of their appearance and their frequency. The frequency in a smaller number of infants with retrolental fibroplasia will be reported as well. The occurrence of capillary and deep cavernous hemangiomas has also been registered.

Own Investigations

Case material

The primary material consisted of 640 premature infants, of whom 293 weighed less than 2,000 g and 347 weighed between 2,010 and 2,500 g. The control group consisted of 186 mature infants (Table 2). All prematures born at a Maternity Clinic in Gothenburg during 1951–54 have been included. The mature infants were born at the same clinic and selected at random. All children (with a few exceptions) were examined by the author at birth and then at intervals of 1–6 weeks. Greatest care was taken to discover angiomas. The period of observation appears from Table 3.

TABLE 1

Location of hemangiomas related to body surface proportions at birth.

	Head–neck	Trunk–buttocks	Extremities
Location of hemangiomas (62 infants with 73 angiomas)	21 (28.8 %)	40 (54,8 %)	12 (16.4 %)
Body surface proportions (LUND & BROWDER)	21 %	32 %	47 %

Results

In 20–25 per cent, equally distributed between premature and mature infants, capillary hemangiomas of the naevus flammeus type were found. There were 10 cases of naevi vinosi. A deep cavernous hemangioma including one finger was discovered in one case. All these angiomas were noted at birth. The naevi flammei regressed spontaneously. The others grew in proportion to the rest of the body. These cases are excluded from the study.

A total of 73 superficial cavernous hemangiomas were discovered in 62 of 826 infants. Eight had multiple angiomas. As a rule the angiomas were small and despite a definite tendency to enlarge they seldom exceeded 2–3 cm in diameter. On first examination they were not always perceptibly raised above the skin surface, but they became elevated after a few weeks and then developed a strawberry-like appearance in most instances.

The localization of the hemangiomas is tabulated in Table 1. Of the 73 hemangiomas, 28.8 per cent were located on the head and neck, 54.8 per cent on the trunk and gluteal region, and 16.4 per cent on the legs and arms. The same table also shows the body surface proportions at birth according to LUND & BROWDER. It is evident that the percentage of hemangiomas are more frequent on the head and neck and especially on trunk and buttocks than corresponds to the regional surface area. The extremities have a lesser frequency of angiomas than was expected on this basis.

Fig. 1 shows the time of first appearance in the 62 cases. Only three were found at birth. Not less than 37 children developed angiomas between the second and the fourth week. Since many of the infants were not examined as frequently after this time, it is possible that some of the angiomas observed later may have appeared during these weeks.

Tables 2 and 3 show the frequency of superficial cavernous hemangiomas in this material. The frequency of angiomas per week has been calculated by expressing the number of individuals with angiomas as a per cent of the number of individuals examined at the beginning of the week. During the following weeks the observed number of cases is smaller because some

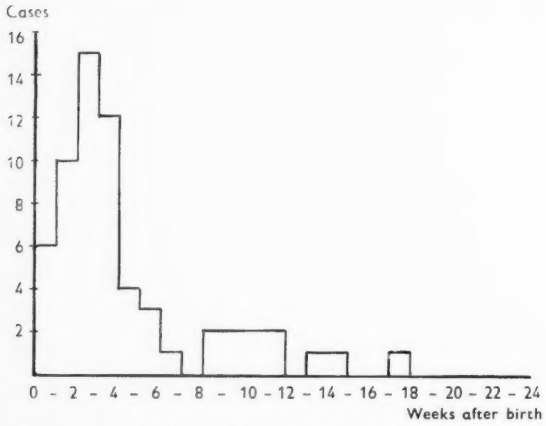

Fig. 1. Time for the occurrence of hemangiomas. (Of six cases during the first week three had angiomas at birth.)

have already developed angiomas and others were no longer under observation. The frequency during the second week is estimated on this lower number of individuals under observation at the beginning of that week. The total frequency (P) is estimated according to the formula: $P = 1\text{-}(1\text{-}p_1)(1\text{-}p_2)(1\text{-}p_3)$, where p_1 etc. is the frequency per week.

The frequency per week is calculated for the prematures divided in two weight groups and for the mature infants. There is no statistically significant difference. At the age of 24 weeks the total frequency of superficial cavernous hemangiomas was almost the same for mature and premature infants

TABLE 2

Number of infants with hemangiomas, number of infants during different periods of observation and frequency of hemangiomas during different weeks.

Time of observation in weeks from birth	Birth weight								
	≤ 2,000 g			2,010–2,500 g			≥ 2,510 g		
	No. cases	Cases w. angiom.	%	No. cases	Cases w. angiom.	%	No. cases	Cases w. angiom.	%
0–	293	4	1.4	347	1	0.3	186	1	0.5
1–	180	4	2.2	328	3	0.9	185	3	1.6
2–	173	8	4.6	268	4	1.5	154	3	1.9
3–	159	3	1.9	211	5	2.4	150	4	2.7
4–	152	1	0.7	165	2	1.2	146	1	0.7
5–	132	0	—	135	1	0.7	144	2	1.4
6–7	112	0	—	119	0	—	141	1	0.7

TABLE 3

Calculated total frequency of hemangiomas up to different points of time from birth and number of cases under observation.

Time of observation in weeks from birth	Birth weight					
	≤2,000 g		2,010–2,500 g		≥2,510 g	
	No. cases	Total frequency	No. cases	Total frequency	No. cases	Total frequency
2	173	3.6 %	268	1.2 %	154	2.2 %
4	152	9.8 %	165	5.0 %	146	5.6 %
6	112	10.4 %	119	6.8 %	141	7.6 %
12	42	13.3 %	33	9.2 %	113	10.3 %
16	20	13.3 %	21	12.9 %	95	11.1 %
20	15	13.3 %	14	12.9 %	85	12.0 %

in different weight groups. The total figures of frequency were between 12.0 and 13.3 per cent. A corresponding estimation for children with birth weights under 1,500 g is not reliable because of too few children under observation.

Thirteen cases of retrolental fibroplasia, all prematures, born during 1948–53 at the same hospital were examined for hemangiomas. It cannot be excluded that small angiomas have been missed in some cases. Two infants had superficial cavernous angiomas. The total frequency of superficial hemangiomas for prematures with retrolental fibroplasia, calculated according to the same formula as for the prematures in general, is 15.4 per cent.

Discussion

Since our experience regarding the incidence of capillary angiomas and the deep cavernous angiomas coincides with other investigators, further discussion on this point is needless. The results of this study of superficial cavernous hemangiomas, however, differs in some respects from published data.

No special tendency for localization to the head could be found. If the proportion of skin surface covering different parts of the body was considered, the trunk was rather apt to be the site of an increase in angioma formation. Our conception of the distribution corresponds to that of RAMBAR. His investigation was similar to ours in that there was no selection of cases and the definition of angiomas was mainly the same. In most other investigations the frequency of facial angiomas has been markedly high. As mentioned above this might be explained by the fact that those whose angiomas caused an esthetic disfiguration were more likely to seek medical

consultation and also because of the confusing nomenclature. Symmetrical localization with many angiomas in the midline, as expressed by STRANDQVIST (1939), has not been observed by us in superficial cavernous angiomas. Only two of 21 angiomas on the head and neck were located in the midline. No localization to the regions of embryonal fissures was noted. The occurrence of deep cavernous angiomas in STRANDQVIST's material might account for this dissimilarity.

In our investigation the superficial cavernous hemangiomas were seldom found at birth. They usually appeared during the 2nd to 4th week. RAMBAR, BLAND-SUTTON and others have also noted this, but with a lesser frequency. The common opinion that they are present at birth is thus not entirely correct. This opinion may possibly be explained by the fact that children are not always closely examined at birth with respect to the occurrence of angiomas and it may be assumed that some of these angiomas found at birth have been deep cavernous or capillary angiomas.

The frequency of hemangiomas in this investigation was nearly equal for prematures and mature infants. No special weight group had a preponderance in angiomas over others. A slightly higher incidence was obtained in the lower weight group during the first weeks, but this difference is not significant. HESS and co-workers have done similar investigations. The difference they obtained is not statistically significant but may have been the basis for the accepted belief that hemangiomas are more common in premature than in mature infants. Moreover, the length of observation was not considered, a factor which is of the greatest importance as demonstrated in this report. Since prematures usually remain longer in the hospital, it is easy to arrive at the opinion that hemangiomas are more frequent in them.

The subsequent development of the superficial cavernous hemangiomas in children is in many cases difficult to judge because almost all received radium treatment at an early age. Since I got to know the reports of LISTER, HOPKINS and others on the spontaneous disappearance of angiomas fewer cases were referred for treatment than previously. It was then shown that in most cases a spontaneous regression occurred which began after the first 6 months. In a recent follow-up (October 1954) I found that some of the untreated angiomas had completely, others almost completely, disappeared towards the end of the second year. There is no doubt that in many cases with small superficial cavernous angiomata good esthetic results are achieved without radium treatment. This is in accord with the known fact that angiomas of this type are rare in adults. Earlier it is hardly conceivable that more than 10 per cent of the children received radium treatment.

Many of the superficial cavernous hemangiomas, especially those located on the trunk and the extremities, do not require radium treatment. They

must, however, be closely observed so that treatment can be introduced if they show signs of rapid growth. LISTER is of the same opinion after having studied the literature, and followed up 93 superficial cavernous hemangiomas. STRANDQUIST and ANDREWS are of the opinion that all angiomas should be treated as soon as possible. This opinion cannot be accepted for all small angiomas that the pediatrician encounters.

Of 13 prematures with retrolental fibroplasia, only two had hemangiomas. REESE concludes that "the incidence of hemangiomas of the skin in premature infants with retrolental fibroplasia is definitely higher than in premature infants in general", on the basis of comparison of the incidence of 15 per cent in his series of prematures with retrolental fibroplasia with the incidence of 3.4 per cent of prematures in general reported by HESS *et al.* In this study the total frequency of hemangiomas for prematures under 2,000 g was 13.3 per cent and for thirteen prematures with retrolental fibroplasia 15.3 per cent. From this study it is hardly possible to state that hemangiomas are more common in premature infants with retrolental fibroplasia.

Summary

The most suitable classification of hemangiomas is that in hemangioma capillare (naevi flammei and naevi vinosi) and hemangioma cavernosum (superficial and deep types), according to ANDRÉN. Of great interest to the pediatrician are the superficial cavernous hemangiomas. They are said to be more common in prematures than in mature infants, and more frequent in children with retrolental fibroplasia.

The primary series consists of 293 prematures with a birth weight less than 2,000 g, 347 prematures with a birth weight between 2,010–2,500 g and 186 mature infants. They have all been followed up from the date of birth and in some cases until the age of six months or longer. The results may be summarized as follows:

1. Capillary hemangiomas appeared in 20–25 per cent. Deep cavernous hemangiomas were most infrequent—only one was found. They were all present at birth; their growth was proportional to that of the skin or they dissappeared spontaneously.

2. The superficial cavernous hemangiomas appeared in 12–13 per cent of the infants, with no significant difference between premature and mature infants.

3. Wide distribution in the skin of the body was noted with a slight predominance on the face and the trunk.

4. Superficial cavernous hemangiomas were rarely present at birth, usually appearing during the second to the fourth week of life and enlarging during the following four months. They resembled strawberry naevi.

5. The superficial cavernous hemangiomas usually showed a tendency to diminish in size after the sixth month, and frequently disappeared in the second or third year. For this reason routine radium treatment is not indicated.

6. In a small group of prematures with retrolental fibroplasia the same frequency of superficial cavernous angiomas was obtained as in healthy prematures.

Les hémangiomes chez le nourrisson prématuré et né à terme.

L'auteur a suivi à partir de leur naissance et dans certains cas jusqu'à l'âge de six mois et plus longtemps, 293 prématurés ayant un poids de naissance inférieur à 2000 g, 347 prématurés pesant à la naissance entre 2010 g et 2500 g et 186 nourrissons nés à terme. Des hémangiomes capillais ont été trouvés chez 20–25 % des cas. Ils existaient tous à la naissance et leur croissance était proportionelle à celle de la peau. Des hémangiomes caverneux superficiels ont été remarqués chez 12 à 13 %, dans une proportion égale chez les nourrissons nés prématurément et ceux nés à terme. Ils n'existaient que rarement à la naissance mais apparaissaient de la 2e à la 4e semaine et grandissaient rapidement pendant les quelques mois suivants. Les angiomes caverneux superficiels ont une tendance à diminuer de dimension après le sixième mois.

Hämangiome bei prämaturen und reifen Säuglingen.

293 Prämature mit einem Geburtsgewicht von weniger als 2000 g, 347 Prämature mit einem Geburtsgewicht zwischen 2010 und 2500 g und 186 reife Säuglinge wurden vom Tage der Geburt aus verfolgt, in einigen Fällen bis zu einem Alter von 6 Monaten und darüber. Kapilläre Hämangiome wurden in 20–25 % gefunden, sie waren alle während der Geburt vorhanden und ihr Wachstum war proportionell zu dem der Haut. Oberflächliche kavernöse Hämangiome erschienen in 12–13 %, gleich oft auftretend bei Prämaturen und reifen Kindern. Sie waren selten während der Geburt vorhanden, doch traten sie während der 2. bis 4. Woche auf und wuchsen schnell während der folgenden Monate. Die oberflächlichen kavernösen Hämangiome zeigen eine Tendenz, nach dem 6. Monat ihre Grösse zu verringern.

Hemangiomas en prematuros y niños a término.

Han sido estudiados 293 prematuros con peso de nacimiento menor de 2000 g, 347 que pesaros entre 2100–2500 g y 186 niños a término desde el primer día de vida hasta los 6 meses de edad o más. Se encontraron desde el nacimiento 20–25 % de hemangiomas capilares cuyo desarrollo fué proporcional al de la piel. Hemangiomas cavernosos superficiales se encontraron en 12–13 % con una incidencia igual en prematuros y nacidos a término. Esta variedad se presentó raramente al nacer, siendo frecuente su aparición entre la segunda y cuarta semana con rápido crecimiento durante los meses inmediatos para luego disminuir de tamaño a partir de sexto mes.

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Children's Hospital
Gothenburg, Sweden

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SUMMARY OF SUPPLEMENT

BCG-Vaccination, Tuberculin Allergy and Tuberculosis in School Children

by HERBERT ENELL

Acta Pædiatrica, Supplement 101

This follow-up study was designed to answer questions concerning the value of BCG-vaccination in children of school age in a country where tuberculosis is a relatively infrequent occurrence.

The first part of this work deals with a general presentation of the problems with a brief history of BCG-vaccination taking into consideration the theories elaborated in answer to these questions. The author also describes the incidence of tuberculosis and the prophylactic measures employed in the primary schools of Stockholm.

Examination was performed on 3,955 children from 7 Stockholm schools: the cases were carefully followed and submitted to tuberculin testing before 1951. Of these, 2,046 received BCG upon their entry into school between 1945 and 1949. In all, 3,112 children were BCG-vaccinated (78.7 per cent) before or while in school. The remainder served as control group, and were chosen neither by chance nor by any rigorous criteria, for this is impractical in Scandinavia in regard to BCG-vaccination.

The author takes into account the existence of exposure to tuberculosis: This is, as one might expect, noticeably higher (28.7 per cent) among those children with natural positive reactions than among those still-positive reacters vaccinated with BCG, and in the other groups (8.7 per cent). Social and living conditions are consistently noted and these factors are considered in relation to medical factors. It seems that BCG-vaccination exists in the same proportion among all social groups in Stockholm. Also, there is no statistical indication of differences due to social causes concerning the diffusion of clinical tuberculosis. Crowded living quarters are in the same proportion among those who have not been vaccinated and it is not noted that children with a positive natural reaction live more often than the others in crowded lodgings.

During the time of observation—in this case, during the time of school attendance—there were no registered fatal cases of tuberculosis in the BCG-

vaccinated or non-vaccinated groups. The time of observation varied from $2^1/_2$ months to 9 years. Among the children with negative tuberculin reactions at the time of their entry into school, clinical tuberculosis exists in the proportion of 1 among those vaccinated to 54 among those not vaccinated, or, if one considers the number of the observed patient years, 1 to 48. In both cases the protection for those vaccinated would be 98 per cent. The 7 children who developed clinical tuberculosis and who had previously been BCG-vaccinated were subjected to more thorough investigation in which the author discusses other associated problems.

Tuberculous allergy and tuberculous immunity are two different things, but from a practical point of view the tuberculin reaction is sufficient in most cases to indicate the immunity acquired against tuberculosis. It is necessary to maintain a tuberculin allergy as long as possible after BCG. Among the children examined there was an average of 1 per cent per year who reverted to a negative tuberculin reaction. At the end of the ninth school year, 91.6 per cent of the children vaccinated during the first school year who had positive reactions still had positive tuberculin reactions. A practically identical result which was very satisfactory from a vaccination point of view was recorded in the different age groups vaccinated at different times.

In the special group of children who were vaccinated at birth or during the first six months of life, there were 85 per cent who, after 7 years, still had a positive tuberculin reaction.

Applying the concepts supported by this study, the author outlines a BCG-vaccination program for the different age groups up to 21 years.

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Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, February 2, 1955

***Symposium:* Treatment of diabetes with especial emphasis on the diet.**

G. Engleson: Dietary treatment of diabetes should aim at sugar-free urine and normoglycemia. This can be attained only by regulation of the diet. The tendency to cancel the free diet has been encouraged by the increasing occurrence of late complications and the experimental support for the opinion that these complications are connected with hyperglycemia. Badly controlled diabetic patients show higher frequency of complications than those who are satisfactorily controlled. The author has arrived at the same conclusions in a study of a Swedish group of diabetics. In this series the yearly growth of the body-length was 3–4 cm before the regulation of the diet and 8–10 cm after this regulation had been introduced. These observations support the studies by *Best* on the growth influence of insulin. An increase in certain lipoprotein fractions in the serum as well as an increased tendency to aneurism-formation has been demonstrated in poorly controlled patients. Theoretically, a high delta-blood sugar should produce a contra-regulation from the adrenal cortex. A hyperfunction may be accompanied by a tendency to retinopathy. There is good reason to aim at only small variations in the blood sugar. Since clinical as well as experimental experiences and theoretical considerations speak in favour of sugar-free urine and normoglycemia, the time has arrived for a revision of the alimentary principles of free diet, which, in our country, were introduced by *Söderling* and *Lichtenstein*.

L. Ström: Free diet is not an uncontrolled diet. Modified normal diet is a more adequate term. Medical control of the diet, whichever type of alimentary treatment one chooses, is necessary. The aim of therapy is to prevent acute and late-occurring complications, but also to promote a state of wellbeing of the child and normal mental and physical capacity. From this viewpoint the free diet means much in deleting the feeling of peculiarity in the life of the child. Also, from a social point of view it is of great importance that the child is made to fit into the family circle. With a restrictive diet there is the risk of hypoglycemia, especially with depot-insulin; the symptoms of hypoglycemia are insidious with bad temper, peevishness, cephalalgia, lack of attention, etc. In the series of diabetic children at the Pediatric Clinic of Karolinska Sjukhuset, we have only seen 4 cases with hepatomegaly, which is a very small percentage in comparison with many other reports. The function of the liver has been normalized in all cases after supply of a sufficient amount of insulin. With the knowledge we now have there is no reason to abandon the principles of the modified normal diet, which for the child implies great relief.

Yngve Larsson: The incidence of vascular disease has been maintained to be higher in diabetics treated with free diet than among patients treated with a controlled diet. Clinical and experimental experiences are referred to. The clinical material on which this opinion is based consists of patients whose diet as well as other forms of treatment have been uncontrolled. This applies to the cases reported by *Engleson*, in which, as a rule, prolonged lack of insulin seem to have occurred. Another series treated with free diet (*Larsson et al.*), with a more adequate insulin supply, shows a lower incidence of vascular complications with statistically significant differences. Experimentally it has been shown that a moderate hyperglycemia produces hyperplasia, while an excessive hyperglycemia produces a degeneration of the beta-cells. Therefore, it is not probable that a moderate and short hyperglycemia will damage the beta-cells. Further support for this opinion is that the need for insulin in patients treated with a free diet is rather constant. The treatment with restricted diet is unphysiological and entails the possible development of disturbances in the physical and mental health of the growing child. Unphysiologic overconsumption of carbohydrates should also be avoided. The author recommended a controlled normal diet, supply of insulin continuously adapted to the need, and active medical control. A postalimentary hyperglycemia up to 300 mg % is accepted, but otherwise normoglycemia, and glycosuria (less than 40 g/day).

Discussion: *Bo Andersson:* It would be remarkable if diabetes should be an exception to the generally accepted rule we follow in the treatment of most diseases; namely, to try to restore a *status quo ante*. A rather constant blood-sugar level is characteristic in healthy persons and is therefore certainly of importance for the diabetics. Before we abandon this general biological principle in treatment and permit a considerably high glycemia, we must know that this regimen does not harm the patient. This proof is still lacking. Those who maintain the thesis of the innocuity of hyperglycemia should give these proofs. I don't believe that the strict principles advocated by *Joslin* can be followed. They are unsuitable in regard to the risk of hypoglycemia. Hypoglycemia can produce encephalopathia and possibly give rise to increased activity of the adrenals, which we believe promotes the occurrence of vascular complications. — *K. Kajser:* If one wishes to eliminate sugar in the urine, it is often necessary to use an intense restriction of the diet and large amounts of insulin. It seems to me not improbable that this very high insulin supply, for years, can be a damage to the body. Perhaps it would be worth while to permit a certain glycosuria with smaller doses insulin. — *H. Berglund:* It has been shown by *Whipple et al.* that after total extirpation of the pancreas the need of insulin in adult men corresponds to 30 I.U. per day. This gives a certain indication of the role of the pancreas in the development of diabetes. The doses of insulin we use in our diabetic patients are thus rather big. Proliferative retinopathy was demonstrated by *Schöitz* before the advent of insulin. Big doses of insulin, therefore, cannot be of etiological importance in the occurrence of this complication. The cause of retino- and nephropathy is unknown. The diet plays a minor role in comparison with other factors. Probably the problem must be solved by animal experiments. Hyperglycemia is however associated with the development of gangrene. After a decrease of the carbohydrate supply the gangrene improves. This is practically the only thing we know about the connection between diet and complications. — *R. Luft:* Pediatricians seem to treat their diabetic patients very carefully. This is probably more important than the difference in opinion between the supporters of free diet and of regulated diet. It has been maintained that a lack of insulin produces an overfunction of the adrenal

cortex. Theoretically, this should not happen: lack of insulin produces hyperglycemia, which scarcely could stimulate overactivity of the adrenal cortex. It has also been maintained that the oxysteroid production of the adrenal cortex should increase with variations in the blood sugar. It is possible that this is true, but these variations would be difficult to demonstrate. — *Y. Larsson:* When the adolescent diabetic is in a very difficult period of treatment, he must drop the contact with the pediatrician. The continuity in treatment is thus broken at a period when medical supervision is highly necessary. Because of this we pediatricians often have to treat children with diabetes far above the 15-year age limit. Collaboration between the internists and the pediatricians is of very great importance. Finally, I want to stress that the fact that some patients do not understand the use of the free diet, is no argument in favour of careful weighing of the different constituents of the food. — *L. Ström:* For a satisfactory treatment it is most important that a good contact is established between the physician and the patient. The patient should feel that he can get in contact with the physician whenever he wishes. In this way the patients follow the recommended regimen more closely. One must help the patient accept the malady and teach him what we know about its nature and its treatment.

J. Bergstedt: **Case of jaundice.**

An 18 month old boy fell ill with diarrhea and jaundice. He was admitted with acholic stools and hepato-splenomegaly. The bilirubin index was 1:60. Thymol test 8, citrate 45 gamma/ml; values speaking in favour of hepatitis. Cholesterol 395 mg %, speaking in favour of occlusion. Wassermann reaction and Weil reaction negative. During the following two weeks the Thymol test was normalized, the protrombin index decreased and did not respond to K-vitamin, tyrosin-cristals were demonstrated in the urine. Fatal outcome in livercoma 3 weeks after onset of the disease. Although the thymol test was normal, there were clincial signs of acute atrophy of the liver.

Discussion: *B. Ivemark:* The pathologic examination showed that the liver was smaller than normally and that the normal liver picture was very undistinct. On microscopic examination the normal cytoarchitecture was changed with central destructions in the lobuli and total degeneration of the livercells out to the zones of the porta. Centrally, the liver parenchyma was replaced by connective tissue. Periportally, there was a rich proliferation of bile ducts and livercells. There were no inclusion-bodies demonstrated and no picture of kernicterus. In summary: a severe diffuse necrosis of the liver with moderate atrophy and histological picture corresponding to a severe acute hepatitis. — *B. Josephsson:* The thymol test is an expression of the relationship between gammaglobulin and albumin. It is supposed to be of diagnostic value in about 90 % and increased thymol values point to damage of the liver parenchyma. Periportally situated hepatitis could give a false normal thymol reaction. The normalizing of the thymol test in this case, although the disease progressed, was probably only an expression of a change in the gammaglobulin: albumin quotient. The tyrosin-cristals in the urine and a decreasing prothrombin index, that did not respond to K-vitamin, pointed, however, very evidently to a severely damaged liver parenchyma.

Á. Lundberg: **A case of peripheral pulmonary stenosis.**

An 11-year-old boy with congenital heart disease that was seen at 20 months of age. After exercise he was a little dyspnoeic and somewhat cyanotic. There was a rough systolic murmur with p.m. in I:2 sin., P:2 was doubled and accentuated. There

was no polyglobulia. Roentgen examination showed bulging of the right ventricle with a decreased blood supply to the lungs. ECG: right ventricular hypertrophy. FCG: systolic murmur over I:2 sin. with amplitude-maximum towards the second sound. Arterial oxygen saturation in the femoral artery was somewhat decreased, 91 %. The peripheral oxygen saturation did not decrease during exercise. Catheterization showed increased pressure (100 mg Hg) in the right ventricle and in the main-stem pulmonary arteries. There was low pressure more peripherally in the pulmonary artery. Angiocardiography: the main stem of the pulmonary artery was rather normal but the branches were hypoplastic with multiple local narrowings with poststenotic dilatations. The pressure was low in the poststenotic dilatations, increased in the hypoplastic parts and was high in the main stem. This type of peripheral pulmonary stenosis is infrequent; one case has previously been observed at the Crown Princess Lovisa's Children's Hospital.

Discussion: *E. Mannheimer:* At Karolinska Sjukhuset we have seen two similar cases. In one of them there was a constriction of the left main stem of the pulmonary artery with an agenesia of the left pulmonary tree. In the other case there was a strong membrane just peripherally to the valvular plane, that produced a gradient between the right ventricle and the pulmonary artery of about mm Hg. The membrane was cut at operation with the consequence that the pressure in the right ventricle decreased to normal values. Peripheral pulmonary stenosis occurs infrequently with very big individual variations. — *Åke Gyllenswärd:* In Upsala we have observed a similar case with similar physical findings as in the reported case. Angiocardiography showed multiple short stenosis in the big as well in the small branches of the pulmonary artery. A sac measuring about 3 × 1 cm and ending blindly extended straight backwards from the principal branch of the pulmonary artery.

O. Quist: **On collum-fractures in children.**

Collum-fractures are infrequent in children. In 10 years, 6 cases were treated at the Crown Princess Lovisa's Hospital corresponding to 2 % of the total number of femoral fractures. An unsatisfactory vascular supply gives rise to retarded healing with risk of coxa vara. Four cases have been treated with stretching and plaster and were healed without complications. One case has been nailed. The end result cannot be evaluated yet. In one case, with fracture through pathological bone, bone chips were transplanted. There was a disturbance of the growth with new bone formation of embryonic character, described by *Bergstrand*, 1930, under the name of "cortical-osteoid".

Discussion: *H. Wahren:* The reported results are very encouraging because collum-fractures in children almost never heal satisfactorily. As a rule both caput and collum are necrotized. In these cases a satisfactory end result can be attained if the necrotic part is removed, the coxal end of the femur is put into the acetabulum and plastered in pronounced abduction in order to produce arthrodesis. Thereafter, a subtrocantheric osteotomy is performed and the leg put into correct position. The growth of the length of the collum caput metaphysis is 6 cm of the total growth. A certain shortening cannot be avoided.

S. M. Härdeling and A. Thilén: **Attempts with antihemophylic globulin.**

The authors have studied the antihemophilic activity of fraction I. (*Cohn*) produced from serum from human postpartum-blood and found that this fraction is considerably larger if it is produced from postpartum-serum than if produced from normal serum.

Discussion: *R. Ordell:* Precipitating antibodies against antihemophilic globulin can appear after parturition, blood transfusion or treatment with antihemophilic globulin and produce a hemophilic picture of disease with life-threatening bleedings. The immediate prognosis seems to be rather unsatisfactory when transfusions and treatment with antihemophilic globulin are without effect. Long-term prognosis is good because of spontaneous hyposensitization. The author has reported a case after parturition. The bleeding-tendency disappeared in this case after one and a half years.

Meeting, March 11, 1955

Symposium on long-acting penicillin in treatment of scarlet fever

***G. Tunewall:* Penicillin concentration in the blood.**

Hemolytic streptococci are sensitive to penicillin to one or a few hundreds of units/ml, and concentrations of this strength ought theoretically to be sufficient in order to control streptococcal infections. In the treatment of the cases from the series that Ström will present later on the patients have been divided into four groups, about 100 each.

P_t: Procain penicillin perorally, 250,000 I.U. × 3 to older children and adults; proportionally smaller doses to smaller children.

P_{d_2}: Injection of DBED-penicillin (Penditan) 600,000 I.U. on the 2nd and the 15th day to older children and adults. Smaller children as P_t.

P_{d_3}: The same injection as P_{d_2} on the 2nd, 8th and 15th day.

P_{dco}: Injection of DBED-penicillin 600,000 + procain penicillin 600,000 I.U. (Penditan comp.) on the 2nd day, solely DBED-penicillin 600,000 I.U. on the 8th and the 15th day. Smaller children as above.

In the P_t group the concentration should be about 1.5 I.U./ml one hour after the intake of the tablet, and 0.03 after 4 hours and at the level of zero after 8 hours, at which time a new tablet was given. The P_{d_2} and P_{d_3} groups have shown concentrations between 0.15 and 0.01 I.U./ml, but surprinsingly often at or in the neighbourhood of the lowest value. The P_{dco} group characterizes itself by a somewhat higher value during the first day; the value is often 1–2 I.U./ml. For the efficiency of the treatment it probably is of importance that, at least during one part of the time, a penicillin level of the blood is attained that can give bactericidal and not only bacteriostatic effect and, in addition, permit the diffusion of penicillin in sufficient quantity into all foci of infection. On the other hand it probably plays a minor role if the concentrations temporarily go down towards zero because it takes a certain time before depressed bacteria regain a productive phase.

***J. Ström:* Clinical results.**

About 100 cases belong to each group of the series. The effect upon the hemolytic streptococci was similar in the different groups; as a rule they had disappeared from the nose and throat after two days. Streptococcus recurrences were, however, rather common (13–20 %) during the hospital treatment, and after discharge the streptococci also returned in a rather high percentage (after 3 weeks in 4.5 % in the Penditan

series, 9 % in the Penditan comp. and peroral tablets series). The antistreptolysin titer increased most markedly in the Penditan groups. Clinically, the result was rather satisfactory in all groups, but the peroral treatment and the Penditan comp. treatment were best, with shorter periods of fever and more rapid decrease of the sedimentation rate and somewhat less number of severe complications. The Penditan injections gave rise to some local reactions in about 1 %, and fever reactions of 38°C and above in 2.7 %.

Discussion: *Lagercrantz.* The results are interesting, especially if they are compared with reports given in the advertisements for the drugs used. Which method has been used in determining the penicillin-content of the serum? — *Tunewall:* The penicillin has been analysed with the lacto-bacillus bulgaricus method. — *Rådmark:* Have allergic manifestations been observed at the Hospital for Contagious Diseases in connection with penicillin treatment? At the skin department of the Garnison Hospital during the last few years 11 cases of cutaneous allergy have been seen in connection with penicillin treatment, with manifestation 14–32 days after start of treatment. In one case anaphylactic shock occurred some hours after injection with Penditan. — *J. Ström:* Several local reactions have been seen and in 18 cases marked fever-reactions occurred. Twice general exanthema of urticarial type have been observed. — *Tunewall:* As regards the results of the treatment and tendency to relapses in the treated group one has to take into consideration the occurrence of penicillinase-producing strains of streptococci, which at present exists in the hospitals, and the possibility that the relapses are new infections with these resistant strains. In one case it has been definitely proven that this was true and it was possible to get the patient free from streptococci only after erythromycin treatment.

J. Lindahl: **Family infections with polio.**

In 71 families, multiple cases of polio occurred. In 51 families one of the children was the first to fall ill, in 20 families an adult was the first who acquired polio. There was no evident relationship between the different types of polio and the morbidity. It has been maintained that the first case in the family has infected the subsequent cases. Previously several reports of the incubation period have been given, varying between 1 and 35 days. In the series at the Hospital for Contagious Diseases, 47 secondary cases have occurred within the first week after the initial case, and within the following week 21 cases. The possibility that there may be a common source of infection of the initial case and so-called secondary cases cannot be excluded. Regarding prophylactic treatment, one may say that when case number 2 and the following cases in the family manifest themselves as rapidly as within 1 week or 10 days, the injection of gammaglobulin in the family contacts cannot have any real value.

Discussion: *Hjärne.* Has infection in physicians or hospital personnel occurred? — *Lindahl:* A female physician fell ill three weeks after she began duty at the polio department of the Hospital for Contagious Diseases. Three cases have occurred among other hospital personnel. — *J. Ström:* It has been discussed that as a prerequisite to being accepted as a hospital nurse at the polio department a certain level of antibodies in the serum should be demonstrable, but then we need about twice the number of applicants for these positions as we have had in order to fill the staff. This condition cannot be upheld.

H. Werneman: **A case of myastenia gravis.**

A nine year old girl was admitted to the Hospital for Contagious Diseases as a case of polio, but this case disclosed itself as a rather typical, progressive myasthenia gravis. She was transferred to the neurological clinic where she was given large prostigmin doses. During her stay at this clinic she had suffered from a very marked mucous secretion in the throat with respiratory distress and she was therefore returned to the Hospital for Contagious Diseases for tracheotomy and respiratory treatment. Because of the physical and mental stress that such a therapy should imply she was instead treated as a bulbar polio: drainage-position, suction of the throat, manual rhythmic pressure on the thorax and nutrition by gavage. With this treatment the patient improved and was happy and out of bed almost the whole day. After 5 months she suddenly died in respiratory failure. The post-mortem examination displayed a thymus of 22 g. Nothing pathological involving the central nervous system, heart and lungs. The sudden fatal outcome could not be explained.

B. Rydenstam: **Severe capillary bronchitis with measles in older children.**

Out of 250 cases of measles treated at Stockholm's Hospital for Contagious Diseases there were lung complications in about 10 %. During this time no case of death occurred. In two cases the condition was very critical for several days, a four year old and a eight year old child displayed clinical and roentgenological signs and symptoms that corresponded with a severe diffuse bronchiolitis. Leukocytosis, increased sedimentation rate and good effect of antibiotic treatment spoke in favour of bacterial secondary infection. Out of the 2,055 cases of measles treated at the same hospital, four have died and three of these were children 2–3–7 years of age. The cause of death was diffuse bronchiolitis.

Discussion: *Lagercrantz:* Has prophylactic antibiotic treatment been used with regard to the incidence of pulmonary complications? — *Ström:* We have made a comparison between a group of cases treated prophylactically and one group without prophylactic treatment and have not found any significant difference between these two groups.

G. Gille: **Purulent meningitis at Stockholm's Hospital for Contagious Diseases, 1942–1954.**

Report was given of 157 patients suffering from purulent meningitis. The etiology has been meningococcus in 56 cases, in 38 cases Haemophilus influenzae, in 23 pneumococcus, and in 12 another bacterial etiology; in 28 cases no bacteriological diagnosis was made. There has been no case of death in meningococcus meningitis since 1947. Among the meningitis of Haemophilus influenzae there was one patient aged 28 and one aged 37 years. The other cases were almost all 2–3 years of age. In 1954, nine cases were treated. The last fatal case occurred in 1949. The pneumococcal meningitis develops usually between 40 and 70 years of age. There has been no case of death since 1949. In the group with another bacteriological diagnosis, the meningits has usually been a secondary complication to a septic disease. The mortality rate was very high in this group. One case of subdural empyema after Haemophilus influenza meningitis was reported, treated with good results by subdural taps.

Discussion: *Barr:* Report of a four-month-old child with pneumococcal meningitis with subdural empyema treated with subdural taps with good result.

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The Danish Pediatric Society

Meeting Jan. 1, 1955

Mental Deficiency and Problems in the Care of Mental Defectives.

Lectures: Jacob Øster, M.D., Andreas Schwalbe-Hansen (Senior Physician), Georg Bredmose (Senior Physician) and Professor Preben Plum.

The minutes of this meeting, including the contributions to the discussion, will be published unabridged in the Scandinavian medical journal *Nordisk Medicin*.

Meeting February 16, 1955
in The Copenhagen County Hospital (Københavns amts sygehus). Hellerup.

Agnete Bræstrup: **The Environmental Conditions of Illegitimate Children at the Age of 5 Years, Born in Copenhagen.**

Approximately one tenth of all children are illegitimate. This figure is fairly independent of the total number of births as increase in the birth rate is accompanied by increase in the number of children born outside marriage. An additional 40 per cent, approximately, of first-born children are born within 9 months of marriage. The data available to illustrate the environmental conditions of illegitimate children as compared with legitimate children are briefly reviewed. Little has hitherto been known regarding the family environmental conditions of illegitimate children during childhood. On the initiative of the Medical Women's Association, the Statistical Bureau of Copenhagen investigated the distribution at the age of 5 years of illegitimate children born in Copenhagen in 1947. The mortality during the first 5 years of life was 7 per cent as compared with an average of 4.5 per cent calculated for the total number of children in the country as a whole. Fifty-five per cent of the children lived with their mothers who had married; at least 32 per cent of these mothers had married the child's father; 17.2 per cent of the children lived in families as adopted children, viz., a total of 82.5 per cent of illegitimate children lived under normal family conditions at the age of 5 years. Of the total number of the illegitimate children 1.4 per cent only lived in children's homes or similar institutions. The remainder of the children lived with their mothers who were still unmarried, with their fathers, with grandparents or were looked after in some other (temporary) way. The number of very young unmarried mothers was striking: 28 per cent were under the age of 19 years. The younger mothers, in particular, had their children adopted while a relatively large number of older unmarried mothers had kept their children and remained unmarried. Four fifths of those mothers who had their children adopted were themselves born outside Copenhagen. (It must be remembered that half of the total female population of Copenhagen is not born in the capital.)

To be published unabridged in the Danish medical journal *Ugeskrift for Læger*.

J. Kringelbach: **Hysteriform Neurosis. Demonstration of a Case with a Surprizing Explanation.**

The patient was a girl, aged 6 years, the second adopted child in a family. The girl had previously shown moderate behaviour difficulties. Three weeks prior to admission, she had been so unreasonable and naughty on her elder brother's birthday that she was finally given a spanking. Since that day, she had been sulky, introverted, prone to attacks of weeping and fury, had refused food and lost weight. On examination, she reacted completely hysterically. On rectal examination, an intrapelvic tumour was revealed. At operation, a dysgerminoma, the size of an orange, was removed with the left ovary and a dysgerminoma, the size of a walnut, was removed with the right ovary. Since operation, she has been pleasant and happy without behaviour problems.

J. Kringelbach: **Disseminated Lupus Erythematosus. Demonstration of a Case.**

The patient was a girl, aged nearly 7 years, who had suffered from skin symptoms for 4 months. These had been regarded and treated as childblains. During the same period, the child had not thrived; she had become increasingly tired and irritable and had had fleeting joint symptoms. Two weeks prior to admission, she had chickenpox. Since then, the general condition had improved somewhat. The examination showed: hypochromic anaemia, leukopenia, increased E.S.R., swelling of various joints, normal AST and ASH, normal urine, normal lung and heart findings, normal ophthalmoscopy. The skin over the knuckles, on the lower limbs and the face showed changes entirely corresponding to disseminated lupus erythematosus with, among other things, typical butterfly marking. "L.E" cells were not demonstrated, a fact which may be explained by the recently sustained infection (stimulation of suprarenal glands) following which an improvement in the general condition also occurred.

J. Gormsen: **Haemophilia with Normal Coagulation Time.**

No report submitted.

J. Kringelbach: **Fibroelastosis of the Endocardium.**

A brief review of the clinical picture was given based upon the available literature. On reviewing the post-mortem records concerning 576 children who died in or who were dead on admission to the Pediatric Department in Gentofte during the period Feb. 1, 1946 to Dec. 31, 1954, two cases of fibroelastosis of the endocardium were encountered and one case of non-inflammatory congenital endocarditis which may be classified in the same group of diseases. The histories of these three cases were reviewed.

Discussion: *Ib Boesen.* Mentioned the case of a boy, aged 6 months, admitted to The Childrens' Hospital, Martinsvej, Copenhagen, where the diagnosis of fibroelastosis in the left side of the heart was suspected after clinical investigation and confirmed on angiocardiography in conjunction with cardiac catheterization which, in addition, revealed an atrial septal defect. Injection of radio-opaque medium in the left atrium showed very slow emptying of the left atrium and the left ventricle on account of practically complete abolition of the contractions of the cardiac chambers involved. The patient was treated with A.C.T.H. (10 mg × 2) for 3 weeks and thereafter with cortisone (5 mg × 2) for 2 weeks. The condition is steadily deteriorating.

B. Hastrup: Neonatal Tetany.

A very severe case of neonatal tetany in a full-term female infant aged 14 days was recorded. The symptoms developed 2 days after breast milk had been supplemented by a cow's milk mixture. Severe generalized, continuous clonic seizures occurred with oedema and peripheral cyanosis. Chvostek's sign was negative and neither carpopedal spasm nor stridor occurred. The serum calcium was found to be 2.3 mg %. During treatment with $CaCl_2$ orally and AT-10 (parathyroid hormone, Bayer), the serum calcium rose to normal values (9–10 mg %). Simultaneously, the symptoms of tetany gradually disappeared completely and did not recur after cessation of the treatment. It was pointed out that neonatal tetany can scarcely be differentiated clinically from seizures of other origin in newborn infants. Carpopedal spasm and stridor are definitely rare symptoms in neonatal tetany. A plea was made for recognition of the supposition that the hypocalcaemia in neonatal tetany is caused by a transient parathyroid insufficiency which probably is caused by antenatal influence of the increased parathyroid function in the mother. This theory is strongly supported by the cases observed where women with primary hyperparathyroidism have given birth to children who developed severe neonatal tetany. In the case recorded, no sign of primary hyperparathyroidism was found in the mother and her serum calcium was found to be at the lower limit of normal. It is mentioned that the low serum calcium perhaps caused a particularly pronounced secondary hyperparathyroidism in the mother.

Discussion: *C. Friderichsen.* Several cases of seizures in newly born infants are probably due to low serum calcium. — *P. Plum.* Has investigated the condition mentioned by C. Friderichsen and, on this basis, is of the opinion that it must be rare.

P. W. Brœstrup: **Report from The World Child Welfare Congress in Zagreb in September 1954 Concerning Children Separated from their Families.**

The congress was arranged by The International Union for Child Welfare. Approximately 350 delegates from 32 different countries took part in the congress, representing child welfare administrators, paedagogic circles, physicians, particularly paediatricians and psychiatrists, a number of psychologists and a series of representatives from private child welfare organizations, the majority of these representing the national member organizations of the Union. The points of particular medical interest were the efforts which are being made in various places to avoid the removal of children from their homes on account of illness and the possibilities of diminishing the disadvantages, particularly the mental disadvantages, of hospitalized children through visits from the parents. Reports were presented from England, Yugoslavia and Roumania concerning attempts at much more extended ambulatory out-patient paediatric activity than we, in Denmark, are used to with "mobile units" consisting of physicians and nurses who could visit the homes and treat children who would otherwise definitely be hospital patients. Blood transfusions were, for example, included in these activities and it was emphasized, particularly by delegates from Great Britain, that the cost of such a service was much less, probably approximately half, than the corresponding cost of hospitalization of the children. Concerning the problems arising from visits to hospitalized children there were fervent adherents to the most extreme viewpoints. In the majority of places, definitely limited visiting hours with definite visiting times from once to twice or thrice weekly are still maintained and in isolated hospitals no visiting was permitted while the children were hospitalized. In other hospitals, visits to the patients were freely permitted and it was maintained that this may be done without inconvenience to the work of the department. Such an arrange-

ment was introduced in The Hospital for Sick Children, Great Ormond Street, London, first as a trial in a single ward and thereafter adopted universally in the entire hospital *at the request of the nurses*. In the University Clinic of Sarajevo, excellent results had been obtained with a system in which visits were freely permitted during ward rounds and examination of the children. This system, we were told, created considerably more confidence and satisfaction on the part of the mothers as regards the fate of their children in the hospital. No report was submitted about detrimental results of extended visits to hospitalized children. B. recommended more propaganda among physicians for congresses of this kind as he considered the participation of physicians in mixed discussions such as these both instructive and valuable for hospital work.

Discussion: *A. Rothe-Meyer.* Does the good service mentioned in connection with Yugoslavia cover the entire country or are certain highly developed centres concerned only, while the remainder of the country does not enjoy this service? — *P. Bræstrup.* The Yugoslav delegates admitted that the latter was the case but it had been necessary to start in this way, among other things on account of the lack of physicians and hospitals. — *A. Rothe-Meyer.* Agreed, in principle, that extended visiting hours were indicated but mentioned that occasionally it might prove advantageous to sever a noxious contact between child and parents. Wondered whether the parents would be able to take advantage of the extended visiting hours. — *P. Bræstrup.* It is perhaps uncertain whether the visiting hours can be utilized but in those places where the system has been put into practice it has appeared satisfactory.

Meeting March 9, 1955
in Queen Louise's Hospital for Children, Copenhagen.

Ib Boesen and Stephan Vendel: **Post-Mortem Diagnoses in 1137 Infants under the Age of 4 Years with Congenital Heart Disease. (To be published in extenso elsewhere.)**

The material differs considerably from that of Maude Abbott, which may be explained, *inter alia*, by the age limits. One hundred and eleven patients died from extra-cardiac causes: other severe malformations, haemorrhages (intracranial, suprarenal), extrapulmonary infections. One hundred and twenty-two were mongols. In about one third of the remaining 904 infants, malformations of the heart were encountered which were theoretically operable considering the possibilities for operation now available (Steno-Fallot's tetralogy, pulmonary stenosis, coarctation of the aorta of "adult variety", defects in the interauricular septum, patent ductus arteriosus). The percentage of operable cases remains unchanged even if infants who died within the first month of life be excluded. Approximately two thirds of the infants died within 5 months of life and approximately 90 per cent within one year of life. Early investigation is thus essential for the timely recognition of these cardiac conditions, i.e. during the first months of life.

Ib Boesen, John Lind, Bjarne Merrild-Hansen, Thomas Rosendal and Ole Storm: **The Diagnosis of Congenital Heart Disease in Early Infancy, Particularly by Means of Cardiac Catheterization and Angiocardiography. Illustrated by Investigations of 43 Patients.**

Out of 43 infants, in whom congenital heart disease was suspected, 9 were examined by venous angiocardiography; 34 by cardiac catheterization combined with selective angiocardiography. All infants were under the age of one year with 3 exceptions. The

oldest of whom was one year and ten months old. Minimum weight of patients subjected to venous angiocardiography was 1.6 kg and to cardiac catheterization 3.2 kg; maximum weight 9.7 kg. One infant died the day after catheterization + angiocardiography, possibly because the patient's condition, already very poor, deteriorated in consequence of the investigation. One patient died suddenly the day after venous angiocardiography without any obviously demonstrable connection between the fatal issue and the intervention. In this connection it should be mentioned that one infant died the day prior to and 2 infants the very day scheduled for the investigation but prior to its performance. Seventeen infants suffered from operable cardiac conditions: 5 Steno-Fallot, 3 pulmonary stenosis, 2 coarctation of the aorta, 3 defect of the interauricular septum, and 4 patent ductus arteriosus combined with septal defect. In 18 infants, defect of the interventricular septum with left–right shunt and hypertension in the pulmonary circulation (>40 mm Hg) was demonstrated. Out of these patients, 5 were in such poor condition that the prognosis would be regarded as hopeless when judged according to general clinical criteria. These cases, therefore, were operated upon according to the method proposed by DAMMAN and MILLER (*Pediatrics* 12: 3, 1953) with constriction of the pulmonary artery. Three of the cases died in connection with the operation and autopsy revealed such small defects in the interventricular septum that it is doubtful whether the left–right shunt caused by the septal defect could have been of an order sufficient to explain the hypertension in the pulmonary artery; the possibility that the poor condition of these infants may more probably be conditioned primarily by disease of the pulmonary vessels should be considered.

Discussion: *Professor Fr. Terkelsen.* In the Thoraco-Surgical Department R, The University Hospital (Rigshospitalet), Copenhagen, 5 infants aged from 6 months to 2 years with defects of the interventricular septum were operated upon. The operation was carried out according to DAMMAN's method with constriction of the pulmonary artery with the object of relieving the overloading of the pulmonary circulation. Two of the infants were discharged well and improved. The remaining 3 died. Autopsy revealed septal defects of from $^1/_2$ to 1 cm in diameter. Despite the smallness of the septum defects, these infants were, nevertheless, in extremely poor condition with pronounced dyspnoea and states of collapse. It may be assumed that the poor conditions and the 3 fatal cases in connection with the operation were caused by the pulmonary changes, probably primarily and accentuated by the presence of the septum defects. — *J. Vesterdal.* Accounted for a personal follow-up examination of the above 2 children who survived DAMMAN's operation. 1. B. R., born 9.6. 1954. Birth weight 1,950 g. The infant did not thrive and suffered from dyspnoea and cyanosis on exertion. At the age of 5 months, the patient was operated upon according to DAMMAN's method. She then weighed 4,300 g. After the operation, the general condition improved and the infant began to thrive. On follow-up examination $1^1/_2$ months after operation, she was not thriving and she had gained only 260 g during a period of somewhat less than 2 months. She is slightly less dyspnoeic than prior to operation and not cyanotic. X-ray examination: configuration and size of heart unchanged but the pulmonary congestion has decreased somewhat. — 2. P. W., born 23.4. 1954. Birth weight 3,050 g. The patient was operated upon according to DAMMAN's method at the age of 7 months. After operation she became somewhat less dyspnoeic. On follow-up examination 3 months after operation she was thriving and had gained 960 g in weight during 2 months. Some dyspnoea present. No cyanosis proper but the colour of the skin is slightly greyish. Cyanosis appears, however, when the child cries. X-ray examination: the relative size of the heart has diminished and the lung markings

regressed considerably. — *H. Baden.* Coarctation of the aorta may be the cause of death in newly born infants and early operation is therefore indicated in selected cases. In the Thoraco-Surgical Department R, The University Hospital, Copenhagen, 2 cases of coarctation of the aorta occurring in infants aged 9 months and 8 months respectively were operated upon. Postoperative course uneventful in the first case. The second infant died on the third day, probably from heart failure. Autopsy confirmed the diagnoses; there were no indications that death was attributable to the operative technique. The two cases may illustrate that operation for coarctation of the aorta in newly born infants obviously is feasible from a purely technical aspect. The prognosis is favourable in the adult variety while in the infantile variety it depends upon the presence of additional abnormalities and the order of these abnormalities. — *A. Tybjærg Hansen.* Was particularly interested in the composition of the autopsy material and the time when death occurred. The distribution of the material differs considerably from the material from The University Hospital, Copenhagen, consisting of about 1,200 patients examined for congenital heart disease in the cardiological laboratory. The prognosis in patients over 2–4 years with defect of the interventricular septum, even extensive, is far better than that in the patients described in the lecturer's material who underwent operation. It appears probable that the septum defect, *per se*, is of lesser significance and that pulmonary hypertension plays the principal role. Catheterization of the heart and other special investigations, frequently including angiocardiography, are necessary in the majority of cases, especially when children over one year and adults are concerned, as the diagnosis must be verified completely and in detail in each individual case, in view of the operative possibilities. The younger the patient the greater the information obtained by angiocardiography. Angiocardiography was performed in approximately $^1/_6$ of the patients in the material from The University Hospital. On account of the great number of patients on the waiting list, first and foremost those children who have survived the first year of life have been examined; on the whole the changes of benefiting from surgical treatment is greater in these children. The problems in establishing the operative indications are not solely technical in nature. It is, however, of great significance to obtain the best information possible concerning the pathological physiology and nosology of congenital heart disease in newly born infants and to establish the relationship of these factors to other age groups. Not until then is it possible to decide if and when surgical intervention is indicated.

Henning Andersen: **Investigation of the Thyroid Function in Children by Means of Radioactive Iodide.**

A graphical demonstration of examples of radioactivity as measured over the thyroid gland and in the urine and saliva was given. In particular, the conditions in children with various types of myxoedema were mentioned: athyreoidism, myxoedema with goitre and hypophyseal myxoedema. In these children, the determinations are in agreement with skin biopsies and determinations of thyrotropin in the serum. The effect of administration of thyroid substance to a patient with normal function of the thyroid gland was demonstrated by a fall of 20 per cent in the percentage of radioactive iodide absorbed by the thyroid gland. Finally, the lecturer gave examples of the employability of autoradiography in patients in whom carcinoma of the thyroid gland was suspected.

Harald Kreutzfeldt
Copenhagen

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ANNOUNCEMENTS

News of the International Children's Centre

The programme of activities scheduled for 1955

The Executive Board of the International Children's Centre met at the Château de Longchamp on December 7 and 8, 1954, with Professor Debré in the Chair.

As a result of this meeting, the final programme of activities adopted by the Executive Board for 1955 follows:

Medical and Social Courses

1. Course on the problems raised by children deprived of normal home environment (January 10 to February 5).
2. Course on Mother and Child Welfare for African midwives at Dakar (January to May).
3. Course of training for kinesitherapists attending to crippled children (February 7 to June 26).
4. Course on medical, social and educational problems raised by children with sensorial disabilities and speech disturbances (February 28 to March 27).
5. Course of Social Pediatrics for physicians (April 18 to July 10).
6. Course on the treatment of poliomyelitis for physicians, organised by the University of Paris and attended by I.C.C. fellowship students.
7. Course on the tropical diseases of the child and their social consequences (September 19 to October 30).
8. Course for social and administrative staff, on mother and child welfare problems (November 7 to December 18).
9. Course for physicians from the Commonwealth attending an improvement course on tuberculosis at the University of Cardiff.

Medical and Biological Research Work

(i) Research concerning the criteria of BCG titration;
(ii) Study of the various BCG vaccines produced by different laboratories.
(iii) Research on the early diagnosis of whooping cough;
(iv) Study of anti-pertussis vaccination.

Documentation Centre and Library

The number of the reviews indexed and of references concerning medico-social, social and psychological questions is to be increased.

The Centre of documentation on medical, social and psychological problems of childhood is to be extended.

Publications

1. The I.C.C. will continue the regular publication of its two reviews, "Courrier" and "Neo-natal Studies".

   The lay-out of the Courrier is to be improved. In addition to original papers devoted to the activities of the I.C.C., the Courrier will carry surveys of topical medical and social questions. It will further comprise two new bibliographical sections concerning social and childhood problems in underdeveloped countries.

2. Five new books will be published:
   (i) The progenesis or the pre-conceptional factors of development of the human being.
   (ii) The leisure-time entertainment of children in isolated rural areas.
   (iii) The deprivation of maternal care.
   (iv) The child and the cinema.
   (v) The gamma globulins and their use in children's diseases.

Activities in Underdeveloped countries

A technical service is to be set up to take charge of preparing, carrying out and coordinating the various studies concerning underdeveloped countries, as well as of organizing a specialized documentation centre.

Medico-Social and Social Studies and Enquiries

1. Study on the growth of the normal child in Europe (Paris, Stockholm and Zurich) and in Africa (Dakar, Kampala).
2. Enquiry on the lot of crippled children in France and Italy.
3. Experiment in training young mothers at a Paris maternity hospital.
4. Study on the lactation of the African mother and its relationship to nutrition at Dakar.
5. Study on the psychological reactions of adolescents to recreational films.
6. Investigation of psychological readjustment of children with motor disabilities.
7. Enquiry on juvenile delinquency in Cameroun and Madagascar.
8. The contribution of the I.C.C. to the work of the Soissons Public Health Centre.

Working Parties and Seminars

1. Seminar on up-to-date treatments of tuberculosis of the child.
2. Working group on BCG immunization against tuberculosis.
3. Working group on the lot of crippled children.
4. Working group on activities in underdeveloped countries.
5. Working group on the growth of the normal child.
6. Working group on the education of parents and teachers.
7. Working group on the psychological reactions of adolescents to recreational films.
8. Working group on Teaching.
9. Working group on Publications.
10. Working group on the Library.
11. Plans for a meeting to study problems concerning the organization of mother and child welfare, prior to the meeting of WHO Committee of Experts.

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BOOK REVIEW

Antibiotica and Chemotherapia: **Advances Vol. I.**

S. Karger, New York. Sw. frs. 52.

The literature on antibiotics and chemotherapy is very great and difficult to survey and therefore summaries of the experiences of the last few years are valuable. The collaborators in this volume have made contributions to the study of chemotherapy themselves and they give a representative report of the new findings. An introduction is written by J. Büchi, Zürich, and deals with the newer development of antibiotics as remedies. The stress has been laid upon the chemical and pharmacological problems. H. Bertelheimer and W. Engert, Berlin, write about treatment of endocarditis lenta. They recommend massive doses of penicillin, even in combination with streptomycin. The newer bacteriostatic remedies seem to be ineffective in endocarditis lenta. S. Helander, Stockholm, writes about combined sulpha treatment which is preferable to single sulpha preparations. E. Rossi discusses antibiotics in pediatrics. He determines the dosage according to the body-surface area. He recommends relatively high doses of water-soluble G-penicillin, f.i. in pneumonia 50,000–100,000 I.U. per kg/bodyweight and day, divided in 2–4 doses, but he warns against procain preparations because these can sensitize the child. Regarding urinary infections Rossi mentions the lack of correspondence between the sensitivity tests and the clinical course, which may be due to a very high concentration of the drug in the urine or can sometimes be explained by (congenital) obstruction of the urinary tract. The good results of intensive antibiotic treatment in purulent meningitis are stressed.

It is significant that the other part of the book is devoted to discussions of the untoward side-effects of the treatment. These are not rare, often severe, and motivate narrow indications for the use of these remedies. P. Retchnick, Geneva, gives a report on a great number of pseudo-membranous enterocolitis due to penicillin-resistant enterotoxin-producing staphylococci. This disease can develop early during treatment with broad-spectrum-antibiotics and is often fatal. Regarding the prevention of this disease and of Monilia infections, the ideal antibiotic treatment is to avoid remedies with the broadest possible effect but rather to demonstrate the pathogenous organism, to determine its sensitivity and to use the antibiotic that has the best effect on the pathologic organism, but the smallest possible influence on the normal bacterial flora of the body. When patients are treated with broad-spectrum antibiotics and complications occur, they should be controlled carefully by repeated laboratory studies so that the treatment may be changed if necessary. In addition one has to take into consideration the allergic factors and the vitamin balance. Regarding the hitherto unsatisfactory treatment of mycotic infections treatment with methyl- and propylparaben seems to be valuable. In the long row of side-effects the authors have not discussed the question of the depressed immunity with antibiotic treatment. Rossi in fact denies the existence of this problem, although the experiences from Stockholm (A. Ström) show that they are important in scarlet fever.

R. Lagercrantz, Stockholm.

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